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Neurophysiology

The communications which are presented here by physiologists and neurologists represent such a wide range of research and offer so much of interest that they may fittingly be introduced by a short review of the more important stages in the development of neurophysiology, a field to which British workers had early made many noteworthy contributions.

In the later years of the last century, attention was particularly focused on the localization of function on the surface of the forebrain, of which there had been no indication till Broca showed that certain functions of speech depend on integrity of a portion of its cortex. It was not, however, till 1870, when Fritsch and Hitzig succeeded in evoking movements of the limbs by stimulation of the cerebral cortex by an electrical current, that the important part which this plays in the higher mammals, and especially in man, was recognized. These observations excited the interest of Ferrier in Great Britain, who, by his early training in physiology and psychology and by his exceptional manual dexterity, was particularly fitted to extend and elaborate them. He succeeded in demonstrating that not only initiation of movement, but also sensation, vision and hearing, are represented in, or related to, separate circumscribed areas of the surface of the forebrain. Confirmation, and in some respects modification, of Ferrier's observations came from his fellow countrymen Horsley, Schäfer, Beevor and others ; in fact, during the succeeding twenty years, the chief contributions to this subject by experimental methods were made by the British school.

But even before it had been shown that restricted areas of the cortex are related to certain functions, Hughlings Jackson, whose teaching has had a profound influence on the development of this branch of neurology, had with remarkable insight discussed at length not where functions can be localized, but the more essential problem of how they are represented in the higher levels of the nervous system.

The next milestone in this chapter of neurology was the series of investigations by Grünbaum and Sherrington on the excitable cortex of anthropoid apes. In addition to providing a more precise scheme of localization of motor functions, these investigations showed that the response of any point to electrical stimulation is not constant and unalterable, but varies with varying conditions of stimulation; in other words, the motor cortex is a plastic organ. All subsequent investigations have confirmed Sherrington's conclusions, but as Jefferson in this number points out in his review of recent work, the conviction has been gaining ground that the exclusive role in initiation and direction of movement hitherto generally assigned to the cortical motor area can be no longer admitted. In fact, clinicians as well as physiologists have come gradually to the belief that even the simplest movement, whether it be voluntary, so-called, or evoked by a stimulus, requires the co-operation of cortical and subcortical mechanisms.

Clinical studies have thrown further light on these and other problems, and especially on those for which a co-operative human subject is essential. Noteworthy among these studies are: the distribution and organization of the sensory receiving areas in the cortex; the mode of synthesis of elementary movements into complex purposeful acts; the recognition and identification of happenings in the outer world or in the subject's own body by integration of messages supplied to the brain, and the use of the conventional symbols of speech for communication with one's fellows. But unfortunately conclusions from clinical observations depend mainly on the study of functions that are disordered by disease and their interpretation is frequently difficult, for the symptoms exhibited by a patient, especially when they are due to injury of the higher and less organized levels of the nervous system, are partly the result of adjustment of intact parts to the specific defect; they rarely give a true and simple picture of the function that is lost.

Though less spectacular, studies of the lower levels of the nervous system have been equally essential to an understanding of how the system works as a whole. Earlier investigations on reflexes mediated through the spinal cord and brain-stem threw much light on the nature of nervous activity of these parts, but it is largely to Sherrington's classical work on the integration of their activities that modern neurology owes its present orientation.

The papers included in this symposium have been contributed by those actively engaged in the study of the subjects on which they write. They deal with almost every branch of neurophysiology, from such fundamental matters as conduction through individual nerve fibres to sensory discrimination at higher levels of the nervous system; from nervous control of the endocrine glands to localization of function in the cerebral cortex.

Much of this has been acquired by the use of new methods which have enabled physiologists to trace and analyze at different levels of the nervous system messages that arrive from the periphery or originate within it. This is well brought out in Eccles' interesting paper on the responses of motoneurones; and Hodgkin's researches on the conduction of impulses, for instance, necessitated the insertion of a fine electrode into a single nerve fibre for the purpose of studying action and resting potentials developed across the membrane on its surface. To observe the effects of stimulation of different parts of the hypothalamus, Harris employed electrodes permanently fixed within it; these could be excited, without interfering with the routine of the experimental animal's life, simply by bringing the animal's head into an electromagnetic field.

All the communications presented here contain matter of special or general interest. The story of the hypothalamus is told from the anatomical side by Le Gros Clark & M. Meyer, and from the physiological side by Harris. The significance of the hypothalamus was for long overlooked, though the fact that its development has scarcely varied in the vertebrate series was suggestive. Now it is recognized as the highest level of the autonomic system. Its intimate reciprocal relations with the cortex enable it, on the one hand, to influence cortical activity itself, and on the other hand to determine the reactions of the ductless glands and other organs to emotional and other higher-level activities.

Another function of the autonomic system is regulation of the flow of blood through different organs. Carmichael, who has already studied it in the distal segments of the limbs, reviews the subject in the light of further observations. In addition to the generally recognized vasoconstrictor reflexes, he finds evidence of vasodilator fibres to arteries, and even that veins, in the peripheries of the limbs at least, may also be under sympathetic control.

Feldberg in a particularly interesting article records experiments which at least suggest that passage of impulses across synapses in the central nervous system may be effected by a chemical transmitter, such as acetylcholine, which Dale has shown to be essential in the autonomic system.

Another noteworthy contribution is Adrian's paper on the basis of sensory discrimination. In addition to a critical review of the subject, he refers to the results of his further studies on the distance receptors, in this instance by experiments on the olfactory system. These show that, as in the case of vision and hearing, recognition and differentiation of a stimulus depends on the characteristic pattern of excitation it forms on the receptor surface.

As facts accumulate it often happens that cherished theories and assumptions must be disenthroned from positions long accorded them, or at least that they must be greatly modified. Jefferson, for example, here brings forward evidence which, though still scanty, suggests that consciousness, in the sense of awareness of surroundings, which has been almost universally regarded as a function of only the highest levels of the nervous system, may be dependent on integrity of certain structures in the brain-stem. If this evidence becomes generally accepted, it will provide yet another instance of a change of outlook brought about with the help of experimental research.

This symposium shows what a wide range of work of this kind is being carried out now in Britain; future developments in this subject should be equally impressive.

Gordon Holmes

Notes on Contributors

PROFESSOR E. D. ADRIAN has occupied the chair of physiology at Cambridge since 1937, and in 1942 was awarded the Order of Merit. Much of his work has been on the function of neurones and on the use of the electroencephalograph. His most recent book, *The physical background of perception*, was published in 1947; other works include *The basis of sensation* (1928) and *The mechanism of nervous action* (1932). In 1945 Professor Adrian contributed to the Neurology number of the Bulletin an article entitled "Physiological Mechanisms in the Brain" (*Brit. med. Bull.* 1945, **3**, 1). Further details of his career may be found in the Notes on Contributors in that number.

DR E. A. CARMICHAEL is Director of the Medical Research Council's Neurological Research Unit at the National Hospital, Queen Square, London. During the Second World War he was Secretary of the Council's Military Personnel Research Committee, and a member of various other committees, among them, the Flying Personnel Research Committee. In 1942, Dr Carmichael, with Dr J. S. Weiner, Dr B. McArdle, and others, began a series of investigations into the effects of high temperatures on the comfort and efficiency of fighting personnel. Research activities on tropical clothing of the wartime Climatic Unit—of which Dr Carmichael was Director—have been described in Dr J. S. Weiner's article in the Personnel Research number of the Bulletin (*Brit. med. Bull.* 1947, **5**, 20). Dr Carmichael's published work includes *On hereditary ataxia and spastic paraplegia*, written jointly with Dr Julia Bell, and published in 1939.

PROFESSOR W. E. LE GROS CLARK is Professor of Anatomy in the University of Oxford. His main interest for many years has been the study of the interconnexions of different parts of the central nervous system by experimental methods. In the past he has concentrated attention mainly on the sensory mechanisms of the brain—in particular the thalamus and the visual system. His earlier studies on the anatomy of the hypothalamus are now assuming a more obvious practical significance, for recent evidence indicates an important functional relationship between this primitive part of the cerebrum and the frontal areas of the cerebral cortex.

DR G. D. DAWSON was educated at Manchester University and carried out research there on recording nerve action potentials, gaining his M.Sc. in 1933. In 1936 he became medically qualified, and after holding various clinical appointments he began work on electroencephalography in 1938 at the Manchester Royal Infirmary. From 1941 to 1944 Dr Dawson was Assistant Director of the David Lewis Epileptic Colony and since then has been on the staff of the Medical Research Council, working in the Neurological Research Unit at the National Hospital, Queen Square, London. In collaboration with Dr W. Grey Walter, he has contributed papers on electroencephalography to the *Journal of Neurology, Neurosurgery and Psychiatry*.

DR JOHN C. ECCLES is Professor of Physiology in the University of Otago, Dunedin, New Zealand. He graduated in medicine in Melbourne in 1925 and came to Oxford, as a Rhodes Scholar, in order to be a pupil of Sir Charles Sherrington. He was a Fellow of Exeter College and later of Magdalen College, and a University lecturer in physiology until he left England in 1937. Professor Eccles, who was elected a Fellow of the Royal Society in 1941, has worked on many aspects of the transmission across the junctional regions between nerve cell and nerve cell (synapses) and between nerve cell and muscle (striated, cardiac and smooth). His recently developed electrical theories of synaptic excitatory and inhibitory processes have aroused much interest and are effectively stimulating research. He is part author of a book, *Reflex activity of the spinal cord* (1932), and the author of over ninety papers in the *Journal of Neurophysiology*, *Journal of Physiology*, *Proceedings of the Royal Society* B, *Nature*, etc.

DR WILHELM FELDBERG's main work has been on the physiology and pharmacology of histamine and acetylcholine. Until 1933 he was lecturer in physiology at Berlin University, which he was forced to leave in that year. He then worked at the National Institute for Medical Research, London, and later at the Walter Eliza Hall Institute, Melbourne, Australia; afterwards he became Reader in Physiology at Cambridge University. Dr Feldberg is now again at the National Institute for Medical Research. In the years after 1933, he demonstrated, with Sir Henry Dale, Professor J. H. Gaddum and, later, with Professor G. L. Brown, the role of acetylcholine as a chemical transmitter across a synapse in the autonomic nervous system and from motor nerve endings to motor end-plates of striped muscle fibres. He was one of the first to demonstrate the release of histamine during the antigen-antibody reaction of anaphylaxis, and with Dr Charles Kellaway, in Australia, showed the release of histamine during poisoning by various snake venoms and by bee venom. With Dr N. Emmelin, Dr Feldberg has recently demonstrated that histamine occurs in high concentrations in the hair fluid of the nettle plant and, with acetylcholine, accounts for the reactions and sensations produced by the nettle sting in the human skin. He has written, with E. Schilf, *Histamin: seine Pharmakologie und Bedeutung für die Humoralphysiologie* (Berlin, 1930), and has translated into German books by Barcroft, Gaddum, and Krogh.

DR G. W. HARRIS obtained his M.D. degree at Cambridge in 1944, and is a lecturer in physiology at that University. He is a member of the Physiological Society, Anatomical Society and Endocrinological Society. He has contributed to various scientific journals papers on such subjects as the innervation and actions of the neurohypophysis and the induction by electrical stimulation of pseudopregnancy and ovulation in experimental animals.

MR A. L. HODGKIN is an assistant director of research in the Physiological Laboratory, Cambridge. He has worked on the mechanism of nervous conduction and his experiments throw much light on the processes underlying the phenomenon. With A. F. Huxley he developed a method of inserting micro-electrodes into the interior of nerve fibre and showed that activity involved a reversal of membrane potential. The present article deals with recent developments in this field. Before the war Mr Hodgkin worked under Barcroft and Professor E. D. Adrian at Cambridge and also spent a year with Dr H. S. Gasser and Dr K. S. Cole in the USA. From 1940 to 1945 he worked on the design of radar in aircraft and was concerned with early applications of the microwave technique. He was elected a Fellow of the Royal Society in 1948, and is the author of numerous articles in scientific journals.

PROFESSOR GEOFFREY JEFFERSON was appointed Hunterian professor of the Royal College of Surgeons in 1942, and in June last year delivered the Lister Oration at the College. He now occupies the chair of neurosurgery at the University of Manchester. Professor Jefferson has gained world-wide recognition in the field of neurosurgery and has published many important papers on the subject. Fuller details of his career appeared in the Neurology number of the Bulletin, to which he contributed an article on head injuries (*Brit. med. Bull.* 1945, **3**, 5).

DR HENRY MCILWAIN previously worked in the Medical Research Council's Unit for Research in Cell Metabolism at Sheffield University, and afterwards carried out investigations of bacterial nutrition with the Council's Department of Bacterial Chemistry at the Middlesex Hospital, London. In 1948 he was appointed to the posts of Senior Biochemist to the Teaching and Research Laboratories, and Senior Lecturer in Charge of Biochemical Laboratories, at the Institute of Psychiatry, Maudsley Hospital, London. Various biochemical studies in connexion with the central nervous system are in progress in the laboratories of the Institute. Dr McIlwain contributed to a previous number of the Bulletin an article entitled "Analysis of Antibacterial Action" (*Brit. med. Bull.* 1946, **4**, 259), with which a more detailed note on his early career was published.

MRS MARGARET MEYER is a research worker who, with the aid of a grant from the Medical Research Council, is engaged in a study of the connexions of the cerebral cortex by the use of silver techniques. For some time she worked in the Institute of Psychiatry at the Maudsley Hospital, London, investigating the anatomical changes in brains of patients who had undergone the operation of leucotomy. More recently, she has been amplifying the results of her observations on the human brain by making parallel studies in the Department of Anatomy at the University of Oxford on the brains of animals which have been subjected to localized lesions of the cerebral cortex.

BRAIN METABOLISM AND ACTIVITY

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1 Changes in blood during its passage through the brain
2 Changes in brain constituents
3 Metabolic potentialities of brain tissues
4 Balance between physiological and biochemical events in brain
5 Utilization of energy-rich compounds
References

In higher animals the main exchange of materials between the brain and the rest of the body is by the blood-stream; exchange by the cerebrospinal fluid is relatively sluggish. The blood supply to the brain is a large one, and if it is interrupted even for only short periods mental activities and the electrical activities of the brain are first disturbed and then cease. Analysis of the blood before and after its passage through the brain shows that changes have taken place in some of its constituents during the passage, and other experiments indicate that the magnitude and type of these changes vary with the activity of the brain. Accurate study of the major exchange occurring during such experiments is relatively recent, and has been chosen as the starting-point of this account, after which some concomitant changes in brain tissue and their relation to the activity of the brain are then considered. Many antecedent studies have of necessity not been described.

1. Changes in Blood during its Passage through the Brain

To determine the over-all metabolism of the whole brain *in situ*, representative samples of all blood entering and leaving the brain are analyzed; surgical techniques may be required in such experiments (Ferris *et al.* 1946; Gibbs, Maxwell & Gibbs, 1947). Simultaneously, the rate at which blood is flowing through the brain is determined; in normal adults this rate is about 600 ml./min. but under varying physiological conditions it can range between 300 and 1,300 ml./min. In a group of normal people the oxygen content of the blood fell from an average of about 20 volumes per cent to about 13 volumes per cent (Gibbs *et al.* 1942). This is a somewhat greater loss of oxygen than the average which is sustained by the blood in passing through the body. The loss of oxygen in the brain is accompanied by an almost exactly equivalent gain in carbon dioxide, that is, the brain's respiratory quotient is close to unity. This suggests that carbohydrate is the main substrate oxidized, and determination of arterial and venous levels of glucose confirms this. Thus one set of experiments showed that of the glucose which was lost on passing through the brains of dogs, 87 per cent could be accounted for by the CO_2 formed, 11·5 per cent by lactic acid, and some 2 per cent by pyruvic acid (Himwich & Himwich, 1946). It is thus unlikely that the brain ordinarily oxidizes any other substrate at a rate approaching that of its oxidation of glucose. Also, if the glucose level of the blood is lowered by insulin, the oxygen consumption of the brain falls, even though the blood contains other oxidizable substrates (Himwich & Fazekas, 1937; Wortis, Bowman & Goldfarb, 1940). The muscles of animals in which this was taking place maintained almost their normal respiratory rate by oxidizing fat or amino-acids; but the brain did not do so. It is presumably such metabolic characteristics which make the functioning of the brain particularly susceptible to hypoglycaemia.

The brain's oxygen consumption corresponds to a respiratory rate of about 2 ml. O_2/g. of brain/hr., or about 3 l. O_2/hr. in the whole brain of a normal adult. Its magnitude can be appreciated by comparing it with the oxygen consumption of the body as a whole, when it is found that in adults at rest the brain takes about one-quarter of the total oxygen used by the body. In infants, whose brain is much larger in proportion to the whole body, the corresponding value is about one-half (Folch, 1947). Brain metabolism is thus not only continuous, but at a relatively high level.

2. Changes in Brain Constituents

The very active exchange of materials which occurs between blood and brain makes it understandable that interruption of the blood-stream should disturb the functioning of the brain. The problem of how this functioning is maintained or disturbed has prompted investigations by other techniques. One technique has involved analysis of the brain itself, in order to discover what changes in its constituents are associated with changes in the materials supplied by the blood, or with changes in brain functioning induced by other means.

Post-mortem changes in brain constituents can be extremely rapid, and the most satisfactory techniques for obtaining the specimens needed in such work are to drop small animals or their heads into liquid air, or to freeze the exposed brain *in situ*. The necessity for such techniques was first shown in 1935 (Kerr, 1935; Avery, Kerr & Ghantus, 1935), when they were devised in order to obtain satisfactory values for the lactic acid, glycogen and phosphocreatine content of brain. Thus values of some 12–30 mg./100 g. brain for the normal lactic acid content of the brains of dogs or cats rose to 65 mg./100 g. brain if cooling was delayed for 2 to 3 seconds, while values for phosphocreatine fell. Such connexion between changes in carbohydrate and labile phosphoric acid derivatives has been the subject of many investigations which have aimed at finding chemical correlates of changed physiological activity, as will be seen in the account which follows.

When dogs were caused to breathe air low in oxygen content, the concentration of inorganic phosphate in the brain rose, while that of phosphocreatine fell (Gurdjian, Stone & Webster, 1944). Cyanides caused the same changes in cats (Olsen & Klein, 1947). Increasing the electrical activity of the brain by means of a variety of convulsants led also to a fall in phosphocreatine, adenosine triphosphate, glucose and glycogen, and to an increase in inorganic phosphate (Klein & Olsen, 1947; Stone, Webster & Gurdjian, 1945). Electrical stimulation produced a 50 per cent fall in phosphocreatine within one second; hexose phosphates and then inorganic

phosphates were formed (Richter & Dawson, 1949). Resynthesis of the phosphocreatine took place within 15 to 45 seconds.

These data can be summarized by saying that respiration maintains, and activity depletes, the labile energy-rich phosphoric esters of the brain. Other changes also are consistent with this general observation. Increased activity or decreased oxygen led to a much greater utilization of glucose and to the formation of more lactic acid than would otherwise have been the case. Decreased activity in anaesthesia or sleep reduced the lactic acid content of the brain (Stone, 1938; Richter & Dawson, 1948a). Increased activity led to increase in free ammonia in the brain (Richter & Dawson, 1948b). The assessing of these various changes is greatly assisted by observations on intermediary metabolisms which are next described.

3. Metabolic Potentialities of Brain Tissues

Independently of the evidence described above, studies with separated tissues and tissue preparations from brain have shown that a major part of their enzymic make-up is related to the metabolism of carbohydrate and labile phosphoric esters. Thus the conversion of glucose to lactic acid is brought about by extracts from brain, and probably proceeds through hexose diphosphate as this compound is converted to lactic acid even more rapidly than is glucose (Ochoa, 1941b). Adenosine triphosphate, cozymase and magnesium ions are required for the reaction to proceed at its optimal rate (Utter, Wood & Reiner, 1945). If fluorides are present to prevent break-down of adenosine triphosphate, esterified phosphate accumulates. Glycolysis is more rapid in the presence of a phosphate acceptor such as creatine (Ochoa, 1941b). Many of the individual stages of phosphorylating glycolysis, observed in other tissues, have also been shown to take place in brain. Hexokinase, phosphorylase and phosphoglucomutase are present (Shapiro & Wertheimer, 1943); phosphoglyceric acid was found to be converted to phosphopyruvic acid, which phosphorylated adenylic acid (Ochoa, 1941a). Dismutations involving fumarate, malate and pyruvate were shown to be dependent on the presence of inorganic phosphate (Long, 1945).

Many enzymes of the oxidative reactions of general schemes of carbohydrate metabolism also occur in brain and result in the formation of energy-rich phosphoric esters. Thus inorganic phosphate, an acid of the tricarboxylic cycle, and an adenosine phosphate and cocarboxylase are required for oxidation of pyruvate by pigeon brain dispersions (Banga, Ochoa & Peters, 1939; Ochoa, 1941b); cozymase, magnesium and cytochrome are also needed (Larner, Jandorf & Summerson, 1949). Such oxidation can yield energy-rich phosphates, esterifying initially some 600 μmol. of phosphate/g. fresh tissue/hr. with a molar ratio of phosphate esterified/oxygen utilized, of about 4 (Ochoa, 1941a). Quantitative data are available on the tissue content of malic dehydrogenase (Potter, 1946), succinic dehydrogenase (Howe & Flexner, 1947) and cytochrome oxidase (Schneider & Potter, 1943).

4. Balance between Physiological and Biochemical Events in Brain

It is immediately understandable that chemical events in the brain should limit physiological ones. But it is observed also that physiological events limit chemical ones: that the normal rate of brain metabolism is below its potential rate; that in sleep it is still further lowered, but that with increased physiological activity it is increased.

The rate of glycolysis is an excellent example of this phenomenon. Rates have been observed for this reaction in carefully prepared homogenates and extracts of brain which give indications of the metabolic potentialities of the tissue in this respect. Rates of glycolysis of 300–450 μmol./g. of brain/hr. are found (Ochoa, 1941b; Utter *et al.* 1945; Elliott & Henry, 1946; Meyerhof & Geliazkowa, 1947). In normal brain the values quoted in a preceding section correspond to the much lower value of 36 μmol./g./hr., but this is very greatly increased in convulsions (Klein & Olsen, 1947).

There is not such a large difference between the potential rates of respiration and those ordinarily realized; homogenates have given rates of approximately 160 μmol./g./hr. (Reiner, 1947; glucose or hexosediphosphate as substrates), or 135–225 μmol./g./hr. (Larner *et al.* 1949; pyruvate as substrate). The normal rate by arteriovenous differences corresponds to 90 μmol./g./hr., and again is increased in convulsions.

The restraint normally imposed on glycolysis operates in separated tissues. The aerobic rate of formation of lactic acid from glucose by slices is normally low—some 15 μmol./g. fresh brain/hr. It can, however, be greatly increased by anaerobiosis, or aerobically by certain reagents of which phenosafranine is an outstanding one. Low concentrations of this substance accelerate glycolysis to values of some 250 μmol./g./hr. (Dickens, 1936). Phenosafranine has now been found to affect a particular metabolic process which the preceding account suggests to be intimately connected with the level of metabolism in brain: this is the formation of energy-rich phosphates from inorganic phosphates during oxidation of pyruvate (Case & McIlwain, unpublished; for analogous observations in kidney preparations, see Judah & Williams-Ashman, 1949). The action of phenosafranine appears to be through its effect on cozymase metabolism (McIlwain, 1949); cozymase is needed for the oxidation. In the presence of phenosafranine, inorganic phosphate and phosphate acceptors remain uncombined, even though oxidation of carbohydrate is in progress. Now inorganic phosphate or phosphate acceptors are reactants in stages of carbohydrate degradation: at hexokinase, which constitutes the point of entry of glucose to glycolysis or oxidation, and again in reacting with glyceraldehyde phosphate. For these reactions, which cannot proceed without inorganic phosphate, phenosafranine provides, or prevents the removal of, phosphate and phosphate acceptors, which would otherwise have been combined. It is therefore understandable that the degradation of carbohydrate should be accelerated.

There is a close analogy in chemical events between the action of phenosafranine and of the convulsive agents discussed above. In those cases the increased physiological activity led to break-down of phosphocreatine and formation of inorganic phosphate and phosphate acceptors. Here also it is evident that these products can themselves stimulate the reactions which lead to their re-formation. A mechanism for controlling carbohydrate break-down by physiological need is thus provided through the balance between energy-rich phosphates and their break-down products.

A further aspect of the stimulated metabolism may be noted. This concerns the balance between the end-products of glucose metabolism, lactic acid and carbon dioxide. It

appears almost certain that in brain, as in general schemes for carbohydrate degradation, these two end-products are the result of two series of reactions which proceed in common from glucose to pyruvic acid. The pyruvic acid may then be oxidized if oxygen is available, or if not, it may form lactic acid. The number of energy-rich phosphate groups which can be generated during catabolism of glucose by these two routes differs widely, varying from 3 to 40 mol./mol. glucose. Thus the situation, observed physiologically, in which most of the glucose catabolized is oxidized completely, could be described as providing the most efficient means of deriving phosphate esters from glucose. In the absence of oxygen this cannot take place, and glycolysis is observed to increase. Aerobically, glycolysis is inhibited in some way; but it can, as was noted above, be released by agents such as phenosafranines. The aerobic inhibition may be mediated also through the availability of phosphate and phosphate acceptors; this and other possibilities have been much debated (cf. Burk, 1939; Lipmann, 1942). Both oxidation and glycolysis require phosphate, but the differential effect—the inhibition of glycolysis aerobically—may be explained in terms of the varying phosphate concentrations required (see Long, 1945) for the different reactions in which it participates.

5. Utilization of Energy-Rich Compounds

Knowledge is very limited of how, in any organ or tissue, the energy derived from metabolic processes is utilized in physiological functioning. In nervous tissues the following findings may be recorded, but at present they can be said to be no more than suggestive. The passage of a nerve impulse is associated with migration of ions. The magnitude of the electric disturbance is related to the magnitude of the ionic change in a way which would be expected were the ion difference responsible for the potential of the discharge (cf. Hodgkin & Katz, 1949). Differential ion gradients can be built up and maintained in separated nervous tissue (Rothenberg & Feld, 1948) and here they are found to require energy-yielding metabolic processes, including glucose break-down (Krebs & Eggleston, 1949). Changes in specific organic constituents are also associated with propagation of nerve impulses. Among these is acetylcholine, and the re-synthesis of acetylcholine by systems from nervous tissue requires an energy-yielding reaction (Mann, Tennenbaum & Quastel, 1938, or the presence of adenosine triphosphate (Nachmansohn & Machado, 1943).

A major limitation in present knowledge of metabolic events in the brain is that the majority of biochemical investigations have been carried out with the organ as a whole of with preparations from relatively large portions of it. The physiologically important events in brain are extremely localized as well as being very rapid. They are undoubtedly dependent on maintenance of general metabolism which it has first been necessary to understand, and much remains yet to be discovered concerning the effects of various agents and conditions on the brain as a whole. But still less is known of the detailed connexions between metabolism and functioning in separated neurones; and relatively little is known of the biochemical peculiarities of different cell types and of different areas in the brain (see, however, Dixon & Meyer, 1936; Elliott, 1948). Feldberg & Vogt (1948) have shown the value of such studies in relation to the organization of the central nervous system. The results of orthodox histological studies also give hints of structural complexities for which the metabolic basis and significance have yet to be found.

It has been necessary, in preparing this account, to select a particular theme which is basic to neurophysiology, and which has recently attracted metabolic investigation. In doing so, many chemical, biochemical, endocrinological and pathological observations with metabolic findings or implications have been omitted. Ultimately the general subject of the utilization of chemically derived energy can be expected to bring an understanding of many observations in these categories. At present, it can be seen that very much more is known about the formation of the energy-rich compounds utilized in brain functioning, and about the control of their formation, than was known a decade ago.

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THE RESPONSES OF MOTONEURONES

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A Antidromic activation of motoneurones
1 Antidromic propagation of impulses
2 After-potential and excitability following antidromic activation

B Monosynaptic orthodromic activation of motoneurones
3 The electrical hypothesis of synaptic transmission
4 Reflexly subliminal activation
5 Reflex discharge of impulses
6 After-potentials and excitability following orthodromic activation of motoneurones
7 Action of repetitive orthodromic volleys on motoneurones
8 Rhythmic discharge of motoneurones
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It may be claimed that virtually all precise investigations on the fundamental responses of the central nervous system have been performed on motoneurones either of spinal or of cranial nerves. Presumably this is attributable to the ease of selective excitation and recording. In particular these neurones can be subjected to monosynaptic excitation by impulses (orthodromic) from the large proprioceptor fibres of muscle and to activation by impulses propagated antidromically up the motor axons. The following account of recent investigations, largely carried out in this laboratory, is restricted to the responses of spinal motoneurones activated thus orthodromically or antidromically. However, this restricted account has some general interest, because, in the absence of precise investigations on other neurones, it has been customary to explain their reactions in terms of the known properties of motoneurones. Since the orthodromic volleys have been elicited from muscle nerves by stimuli not stronger than twice threshold, they have been virtually restricted to the largest proprioceptor fibres, and tests with graduated stimuli have established that all the synaptic excitatory actions described in Section B of this paper are attributable to these large fibres.

Since motoneurones are buried in the central nervous system, their electrical responses may conveniently be led off by a fine (50 μ diameter) needle electrode insulated except at its tip. Such a micro-electrode can be inserted close to a motoneurone or group of similar motoneurones (a motor nucleus), the other leading electrode being an indifferently placed large metal plate. Alternatively, the more prolonged electrical responses of motoneurones may be recorded from the ventral root, whither they have spread electrotonically. Both methods of recording inevitably introduce distortions. The interpretation of the " focal potentials " recorded with a micro-electrode in nerve tissue is now well understood (Barakan, Downman & Eccles, 1949; Brooks & Eccles, 1947; Lorente de Nó, 1947a). A positive focal potential (micro-electrode positive to the indifferent) indicates that to a preponderating extent current is flowing outwards across those nerve cell membranes (of axon, soma or dendrites) in close proximity to the micro-electrode, i.e., that they are " sources " for extrinsic current flow. Conversely a negative focal potential indicates the preponderance of " sinks ".[1] Since under the basal conditions for an experiment extrinsic currents may be flowing (e.g. due to injury), the positive or negative focal potentials recorded on activation do not signify absolute levels of " source " or " sink " respectively, but merely the change from the basal level.

There has been good agreement between the three methods that have been used to test the excitability of motoneurones: direct electrical stimulation through a buried micro-electrode; excitation by a monosynaptic orthodromic volley; and excitation by an antidromic volley fired up the motor axons. In the two former, the excitability is judged by the size of the spike discharged along the motor axons, in the latter by the size of the " soma spike " focally recorded close to the motor nucleus (see Section A1 below).

It is not possible in this brief summary to give a comprehensive treatment of the experimental investigations. Each section gives the explanations or hypotheses that have been developed and the simpler experimental tests that have been applied. In developing these hypotheses it has been assumed that the surface membrane of the nerve cell body (soma) and of its dendrites has electrical and excitatory properties *essentially similar* to that of a nerve fibre (non-medullated), and that the special features are mainly geometrical. However, it has been necessary to postulate some quantitative modifications of properties, e.g., that the soma and dendrites have slower electrical responses than the motor axon, and also larger positive after-potentials. This treatment is sound methodologically, for it ensures that additional postulates are introduced only when all attempts at an explanation have

[1] The term " source " refers merely to the flow of electrical current outwardly from the cell membranes into the external conducting medium, i.e., the cell membrane in such an area is regarded as a " source " for current flow; conversely it is a " sink " when electrical current is flowing from the external medium inwardly across it.

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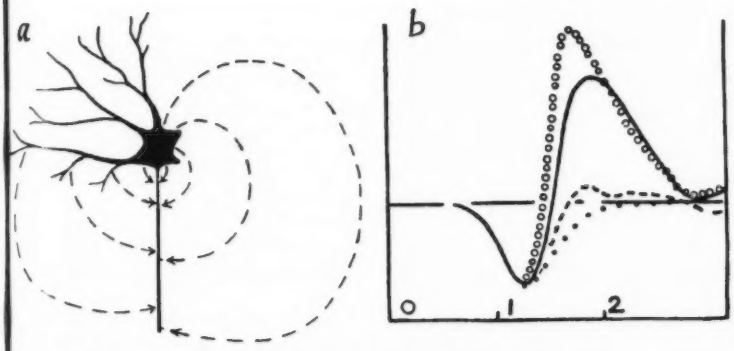

FIG. 1a. Diagram of external lines of current-flow generated by an antidromic impulse that has reached the axon hillock of a motoneurone. On the right the lines are drawn from the soma only, but on the left dendrites are drawn and lines are shown running from them

FIG. 1b. Continuous line shows a record of potential set up by a maximal antidromic volley in quadriceps nerve and recorded by micro-electrode just ventrolateral to quadriceps nucleus. Broken line and line of circles show, respectively, antidromic potential after conditioning depression by a preceding antidromic volley, and after conditioning facilitation by an orthodromic volley. For significance of dotted line see text. Time-scale in msec. with zero at time of stimulus

failed without them. The danger of development of unnecessary *ad hoc* hypotheses is thereby minimized.

A. ANTIDROMIC ACTIVATION OF MOTONEURONES

1. Antidromic Propagation of Impulses

As an impulse propagates antidromically up a motor axon to its motoneurone, the positive focal potential recorded by an adjacent micro-electrode shows that the soma and dendrites of the neurone form a source for currents flowing back into the sink on the axon (fig. 1a), just as occurs from regions ahead of a propagating impulse in a nerve fibre (Barakan *et al.* 1949; Brooks & Eccles, 1947; Lorente de Nó, 1947a). A special feature, however, is introduced by the enormous expansion of surface membrane that begins at the axon hillock as the axon flares out to the soma and dendrites. This geometrical feature provides a satisfactory explanation for the blockage of antidromic axon-soma transmission that occurs with a large proportion of motoneurones (Barakan *et al.* 1949; Brooks & Eccles, 1947; Lloyd, 1943; Lorente de Nó, 1947a); for the area of the source of the soma and dendrites may be so large that the local circuits of current flowing to the axonal sink (fig. 1a) fail to depolarize the soma to that critical degree at which invasion of the impulse occurs. Even when the antidromic impulse does invade the soma and dendrites, the low safety factor in this invasion is evidenced by a brief delay (cf. fig. 2b) of about 0.1 to 0.3 msec. (Barakan *et al.* 1949), which presumably is attributable to slowed propagation into the expanding surface.

As would be predicted, antidromic axon-soma propagation is facilitated (figs. 1b, 2a) by the partial depolarization of soma and dendrites produced by subliminal orthodromic activation (Barakan *et al.* 1949; Brooks & Eccles, 1947; Lloyd, 1943; Renshaw, 1942), and is depressed (fig. 1b, broken line) during the increased polarization (positive after-potential, see Section A2) following the propagation of one or more impulses over the soma and dendrites (Barakan *et al.* 1949; Brooks, Downman & Eccles, 1950a; Lloyd, 1943; Renshaw, 1942, 1946). The facilitation of antidromic transmission not only shortens the delay in axon-soma transmission (cf. the earlier origin of the negative spike, line of circles, in fig. 1b), but also relieves the blockage at many axon-soma junctions. Conversely the depression causes antidromic blockage at many junctions and increases the delay at those junctions still traversed. Thus the focal spike potential set up by an antidromic volley is divisible into a labile component generated by impulse propagation over the soma and dendrites and

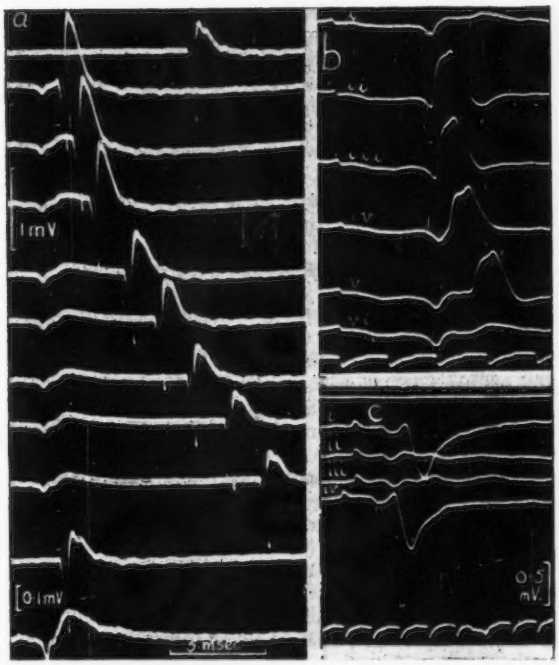

FIG. 2a. Records at top and second from bottom show focal potential set up in quadriceps nucleus by a maximum antidromic volley. Main series from below upwards shows progressively increasing facilitation of the negative (soma) spike as antidromic volley is moved earlier, relative to quadriceps afferent volley. Lowest record shows, at higher amplification, response to quadriceps afferent volley alone (subliminal reflexly)

FIG. 2b. Records i and ii show part of a series of antidromic focal potentials in which an antidromic volley set up by a slightly (1%) stronger stimulus always generated a larger potential, ii, which was not present with a weaker, i. It is concluded from this all-or-nothing behaviour that this additional potential is generated by the antidromic invasion of a *single* motoneurone. Record iii shows a small terminal change invariably produced by the conditioning depression of a preceding antidromic volley, while with records iv and v are seen two stages in lengthening of axon-soma delay before the final failure of antidromic transmission into the soma of that motoneurone, seen in record vi. Time in msec.

FIG. 2c. Antidromic focal potentials from single motoneurones as with records of fig. 2b, but showing the more usually observed positive potential (records i and iv). Antidromic stimuli for records ii and iii 1.1% weaker. Time in msec.

a non-labile component (approximately shown by dotted line of fig. 1b) due to the initial axonal component (Barakan *et al.* 1949).

The spread of the antidromic impulse over the soma and dendrites presumably is by " local circuit " action, but the fine dendritic terminals are apparently not invaded because the focal potentials recorded in the field around the motor nucleus indicate that the dendritic terminals continue to act as " sources " throughout the whole invasion process (Barakan *et al.* 1949). Possibly the profuse branching and diminishing calibre of the dendritic branches cause the invading impulse to slow and die out before reaching the terminals. It may be doubted (cf. Barakan *et al.* 1949) if much significance can be attached to the dendritic propagation velocity of 2 metres per second given by Lorente de Nó (1947a).

It is usually possible to find a position of the micro-electrode such that it records the electrical response of one motoneurone, to the relative exclusion of all others. The records so obtained give the simplest illustration of the above propositions concerning antidromic propagation. Figure 2b shows the brief initial positive wave (soma and dendrites as source) followed by the negative wave due to invasion of the soma and dendrites. The spike so generated is about 1 msec. in duration, which is much longer than the axonal spike. During the depression set up by a conditioning antidromic volley antidromic axon-soma transmission is not blocked but is slightly delayed and the terminal phase of the soma spike potential is altered, possibly owing to an increased failure of propagation into dendritic terminals. In fig. 2b, after the records i to iii, a progressive axon-soma blockage developed (presumably due to mechanical damage by the micro-electrode), as is revealed by a lengthening of axon-soma delay. The longest delay (0.6 msec.) is shown in fig. 2b, v, and thereafter permanent blockage supervened. It is to be noted that, even after such a long delay, there is a normal soma spike potential (cf. v with ii), i.e., once the antidromic invasion has surmounted the critical region of low safety factor at the axon-soma junction, it proceeds at least as far as the dendritic terminals with a much higher safety factor, as would be expected on the local-circuit theory of propagation.

Usually (Barakan *et al.* 1949) single motoneurones have given a positive soma spike potential (fig. 2c), i.e., the inverse of that in fig. 2b. This is attributable to the micro-electrode lying close to an injured area of the neurone. Antidromic invasion of the remainder of the neurone diminishes the flow of injury currents into the region of the micro-electrode and hence will be recorded as a transient positivity, much as occurs with peripheral nerve in a like situation (Lorente de Nó, 1947b).

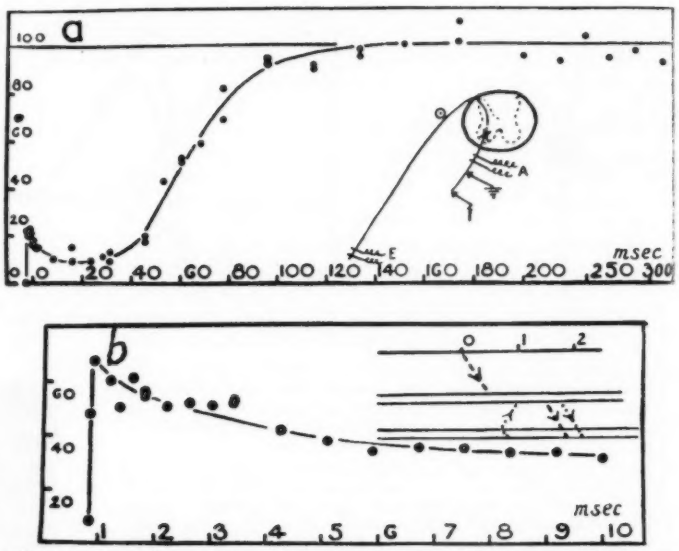

FIG. 3a. Inset diagram shows approximate position of electrodes, E being on the gastrocnemius-soleus nerve, while antidromic stimulating electrodes A are on isolated 1st sacral ventral root. Earth- and grid-leads to amplifier pick up the reflexly discharged spike responses more distally along that root. The testing stimulus through E is applied at various intervals after the conditioning stimulus through A, and its reflex spike response is plotted as a percentage of its mean reflex spike. Abscissae give stimulus intervals

FIG. 3b. Plotting as in fig. 3a, but abscissae are the calculated intervals at the axon-soma junctions between arrival of the antidromic volley and emergence of the testing reflex discharge. Inset diagram gives basis of this calculation (see Brooks, Downman & Eccles, 1950a, for details)

2. After-Potential and Excitability Following Antidromic Activation

Following antidromic activation, motoneurones show a large positive after-potential and an associated depression of excitability (Brooks *et al.* 1950a; Gasser, 1939); these are analogues of the positive after-potential and the subnormal state of peripheral nerve. The potential and the depression run virtually identical time-courses (fig. 3a; and Brooks *et al.* 1950a; Gasser, 1939), decaying from a maximum at about 20 msec. so as to disappear just beyond 100 msec. This time-course is somewhat slower than in peripheral nerve, but the greater size of the two effects provides a more striking difference.

It appears that two distinct processes are responsible for the decrementing after-negativity that immediately follows the soma spike potential and passes over into the after-positivity (Brooks *et al.* 1950a).

(i) In those neurones invaded antidromically there is evidence of a negative after-potential and associated phase of relative supernormality, i.e., of lessened subnormality, thus differing from peripheral nerve in that the excitability is always lower than normal, being supernormal merely to the subsequent depression.

(ii) Those neurones not invaded antidromically pass immediately into a phase of supernormal excitability, which decays rapidly and largely disappears in 10 msec. (fig. 3b). Any such neurone will have been depolarized to a subliminal extent by its antidromic impulse, i.e., it will be in a catelectrotonic state and hence will be supernormally excitable, the decay of this supernormality presumably indicating the time course of decay of the catelectrotonus. Thus the after-negativity would be compounded of a negative after-potential of the invaded motoneurones and a catelectrotonus of the uninvaded.

As shown in fig. 3b the uninvaded motoneurones show their maximum reflex excitability in less than 1 msec. after the arrival of the antidromic impulse at the site of its blockage

(Brooks *et al.* 1950a; Lloyd, 1943). A value as low as 0.7 msec. has been recorded. Thus the facilitated reflex discharge is propagated outwards almost as soon as the axon has recovered from its absolutely refractory period. On the other hand, when the motoneurones are invaded antidromically, they appear to be inexcitable by any test for at least 1.3 msec. and do not recover from their relative refractoriness until about 5 msec. The overlapping supernormal and subnormal states make these determinations inaccurate, but such complications are inherent in any method of determining neuronal refractory periods. Other methods of testing for refractoriness have to contend with additional complications.

B. MONOSYNAPTIC ORTHODROMIC ACTIVATION OF MOTONEURONES

3. The Electrical Hypothesis of Synaptic Transmission

Almost all the experimental data in the sections that follow are satisfactorily explained by the electrical hypothesis of synaptic transmission (Eccles, 1946b, 1949); hence a brief preliminary account is desirable.

As a presynaptic impulse propagates up to a synaptic knob, this knob will be first a source (fig. 4a) and then a sink (fig. 4b) for currents flowing in extrinsic circuits to that presynaptic fibre upstream. It is postulated that a significant fraction of these currents loops through the post-synaptic membrane and hence will in the second phase (fig. 4b) exert a catelectrotonic action on the post-synaptic membrane immediately subjacent to the knob. It is further postulated that this catelectrotonus (C.) is intense enough to set up an active response of that membrane—presumably by activation of the sodium carrier mechanism (Hodgkin & Katz, 1949). A synaptic knob is so small (about 2 μ in diameter) that this post-synaptic activated area is far below the size at which a self-regenerative action would ensure its growth to a full-sized propagating impulse. Hence there will be merely a local response (L.R.) persisting for about the duration of a spike potential (about 1 msec., see Sections A1 and B5), during which time the synaptic knob will act as a sink (figs. 4c, 4d) through which other regions of the post-synaptic membrane discharge, and thus develop a catelectrotonus. When the sink is no more, this catelectrotonic surround passively decays with the electric time constant of the post-synaptic membrane, being responsible meanwhile for the facilitation phenomena; hence it may be called the facilitation potential (F.P.). Alternatively, if many closely adjacent knobs are activated at the same time, then the flow of local current from the interposed areas of the membrane into the mosaic of sinks (post-synaptic L.R.'s) may be adequate to cause activation of these areas, i.e., these L.R.'s will spread and fuse, thus growing up to an impulse propagating over the surface of the motoneurone and down its axon. In this way a reflex discharge is generated.

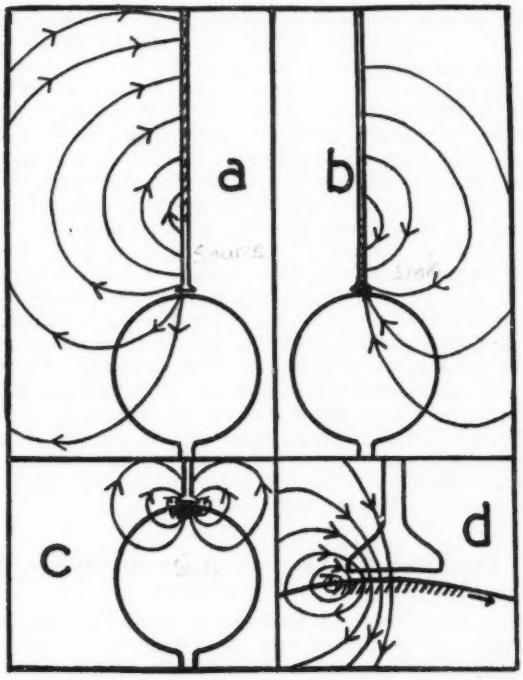

FIG. 4. Schematic representations of presynaptic fibre and motoneurone with lines of current-flow generated during synaptic transmission (see text)

4. Reflexly Subliminal Activation

A single orthodromic volley sets up in the motoneurones two closely related events—an increased excitability and a negative potential. The increased excitability is shown (by means of the three standard testing stimuli, direct, antidromic (fig. 2a), and monosynaptic orthodromic) to reach a maximum in little more than 1 msec. after the arrival of the orthodromic volley in the motor nucleus (Brooks & Eccles, 1947), and thereafter it decays with a half-time of about 3 msec. (Brooks & Eccles, 1947; Eccles, 1946a; Lloyd, 1946).

The negative potential, recorded after electrotonic spread along the motor axons to the emerging ventral root, has a rather slower time-course, rising to its summit in about 2 msec., and decaying with a half-time of about 5 msec. if care is taken to record from the root close to the spinal cord (fig. 5a) (Brooks, Downman & Eccles, 1950b; Brooks & Eccles, 1947; Eccles, 1946a). On the other hand, although having an identical latent period, the negative focal potential recorded with the micro-electrode placed just ventrolateral to the quadriceps nucleus has a faster time-course, attaining its summit in about 1 msec. and decaying with a half-time of about 1.5 msec. (fig. 5b). There is evidence that, on account of the asymmetry of quadriceps motoneurones, a microelectrode in this position is favourably placed for recording currents flowing from the dendritic terminals and axon into the soma and proximal dendrites (Barakan *et al.* 1949), i.e., a negative potential there signifies a sink on the soma and dendrites. The discrepancy between the time-courses of the potentials recorded in these two ways can plausibly be attributed (cf. Brooks & Eccles, 1947) to distortion of the actual potential change of the motoneurone, which would run an intermediate time-course, and so be comparable with the facilitation curve (cf. fig. 10b in Brooks & Eccles, 1947). Thus, on this interpretation, the potentials recorded either focally or from the ventral root have a common origin in the depolarization process (L.R. plus F.P.) which is generated in motoneurones by synaptic stimulation and which decays with

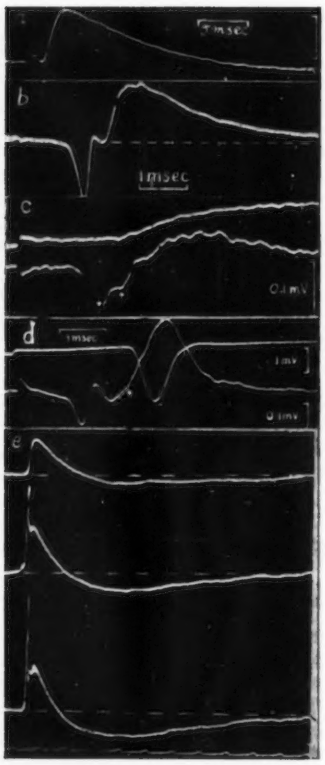

FIG. 5. Synaptic potentials set up by single orthodromic volleys and recorded as follows :

- a : after electrotonic spread to the emerging ventral root
- b : by a micro-electrode just ventrolateral to motor nucleus (quadriceps)
- c : recorded as in a and b for identical orthodromic volleys in same preparation. Note identical latent periods for the two synaptic potentials (lower one begins at second arrow, first arrow showing time of arrival of sink of orthodromic volley at presynaptic terminals)
- d : as in b, but with synaptic potential generating reflex discharge of a volley at arrow. Record of volley in ventral root is shown by inverted spike
- e : synaptic potentials recorded as in a, but for progressively larger orthodromic volleys in quadriceps nerve, the upper record being a pure synaptic potential and the two lower having reflex spikes superimposed. Note the later after-positivity

a half-time of about 3 msec. This rate of decay is much slower than is observed with catelectrotonus of the motor axons, but such observations are complicated by the myelin sheath and the nodes of Ranvier. As yet the rate of decay of a catelectrotonus set up directly by an electrical pulse has not been determined for motoneurones, but it is to be noted that the facilitation process (attributable to a catelectrotonus) generated by a blocked antidromic impulse (see Section A2) decays at a rate comparable with the above facilitation process. Recently it has been suggested (Lloyd & McIntyre, 1949) that the " focal synaptic potential " is generated presynaptically. However, it has been pointed out that there is much evidence against this interpretation (Eccles, 1949), and that the only supporting evidence may be other wise interpreted (Brooks *et al.* 1950b).

As the presynaptic volley propagates up to the motor nucleus, it generates the initial diphasic wave (positive-negative) of the focal potential, and hence gives opportunity for precise determination of the synaptic delay. If this is measured between the arrival of the " sink " phase of the presynaptic volley at the motor nucleus and the onset of the " sink " phase in the motoneurone, i.e., of the negative potentials recorded either focally or from the ventral root, it has a duration of only 0.3 to 0.45 msec. (figs. 5c, 8b).

When the testing orthodromic volley is in a nerve synergic with one carrying a conditioning volley which alone evokes a large reflex response, it has been found that, with very short volley intervals, the facilitated spike may be discharged as a double wave (Brooks & Eccles, 1948). It appears that two distinct facilitation processes are involved, an initial α process which decays so rapidly that it disappears at a volley interval of about 1 msec., and a β process characterized by a longer synaptic delay and the much slower rate of decay already described. An explanation of these two facilitation processes is provided by the electrical hypothesis of synaptic transmission, for the α process has precisely the characteristics that would be given by the initial excitatory effects, C. and L.R., while the β process is attributable to the F.P. (Brooks & Eccles, 1948 ; Eccles, 1949). The α process of facilitation has previously been known as the detonator action.

5. Reflex Discharge of Impulses

Focal recording (figs. 5d, 8b) shows how the reflexly discharged impulse arises as a sudden upward inflection in the negative (synaptic) potential (Brooks & Eccles, 1947), and a comparable observation may be made with the synaptic potential recorded from the ventral root (Brooks *et al.* 1950b ; Eccles, 1946a). There is a delay of from 0.2 to 1 msec. between the onset of the synaptic potential and the initiation of the impulse. This value, when added to the synaptic delay determined for the synaptic potential (see Section B4), gives the delay in initiating the reflex discharge of an impulse, which would thus have a minimum value of about 0.6 msec., and a maximum of about 1.5 msec. Such a range of values would be expected if the reflex discharge arises by the spread and fusion of initially discrete L.R.'s having a duration of about 1 msec. If allowance be made for the asynchronism of the individual units, the focally recorded spike potential of discharging motoneurones has a duration of about 1 msec. (fig. 5d), which agrees well with the antidromic spike duration (figs. 1b, 2b). According to the local circuit theory of propagation, an impulse generated in the soma by synaptic excitatory action would readily propagate on to the axon and would not have the low safety factor characterizing transmission in the reverse direction (see Section A1).

6. After-Potentials and Excitability Following Orthodromic Activation of Motoneurones

When monosynaptic orthodromic activation has generated the discharge of impulses from motoneurones, it would be expected that a positive after-potential of the motoneurones would ensue, just as occurred after invasion by an antidromic volley. This is shown in fig. 5e, but a smaller positive after-potential running the same time-course is seen to follow a

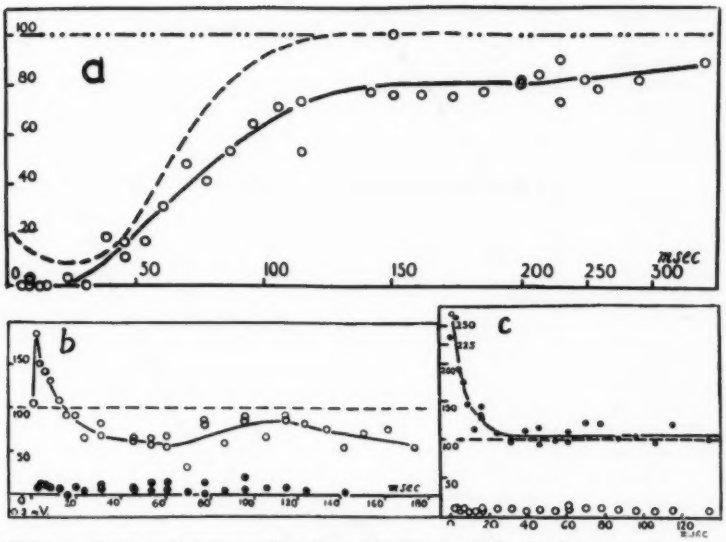

FIG. 6a. Plotting of testing reflex spike response as in fig. 3a, but the conditioning volley is a similar orthodromic volley. The broken line shows the curve of fig. 3a (same experiment)

FIG. 6b. As in fig. 6a—same experiment, but conditioning orthodromic volley so small that it evoked little or no reflex response. Filled circles show the sizes of these conditioning spikes also calculated as percentages of the mean control value for the testing reflex spikes and placed at abscissal values for corresponding testing responses

FIG. 6c. As in fig. 6b—same experiment, but with conditioning orthodromic volley in an afferent nerve (lateral gastrocnemius) synergic with that conveying the testing volley (medial gastrocnemius). Open circles give conditioning spike responses as in fig. 6b

synaptic potential on which no reflex discharge is superimposed. The superimposition of a reflex discharge merely adds to the positive after-potential.

The excitability of motoneurones during these positive after-potentials has been tested with monosynaptic orthodromic volleys (Brooks *et al.* 1950b; cf. Bernhard, 1947). When the testing volley was in the same afferent nerve as the conditioning, there was a very deep depression at 10 to 30 msec. (complete suppression of reflex discharge), and, initially, recovery occurred along much the same time-course as after antidromic activation of these motoneurones (fig. 6a). However, unlike the latter, this phase of recovery was always incomplete and was followed by a prolonged slow recovery of excitability persisting for at least one second. A similar, but usually less intense, depression with two-stage recovery was observed after a conditioning volley which was so small that it evoked little or no reflex discharge (fig. 6b). Presumably the initial phase of depression (i.e., up to about 100 msec.) is attributable to a subnormal state of the motoneurones associated with the positive after-potential, and is identical with that induced by antidromic invasion. When the conditioning volley sets up no reflex discharge, it will still, according to the electrical hypothesis (see Sections B3 and B4), set up local responses (L.R.'s) under the activated synaptic knobs and these areas would be expected to develop positive after-potentials and the associated depression. In accordance with this explanation little or no reflex depression was observed when the " reflexly subliminal " conditioning volley was in a different, but synergic, nerve from the testing volley (fig. 6c). The small depression then sometimes observed (Brooks *et al.* 1950b) presumably is attributable to a spreading anelectrotonus from the localized areas of positive after-potential. On the available evidence the prolonged phase of depression is located presynaptically, for it is never observed when testing by a synergic orthodromic volley.

7. Action of Repetitive Orthodromic Volleys on Motoneurones

The response to repetitive synaptic bombardment is of great interest because it would normally be produced by receptor organ discharges, and, if intense enough, it gives rise to rhythmic discharges of motoneurones. Repetitive orthodromic volleys are relatively ineffective in building up synaptic potentials by summation whether recorded focally or from the ventral root.[2] Even at frequencies as high as 500 per second, summation gives a transient maximum which at most is little more than

[2] Eccles & Rall, unpublished observations

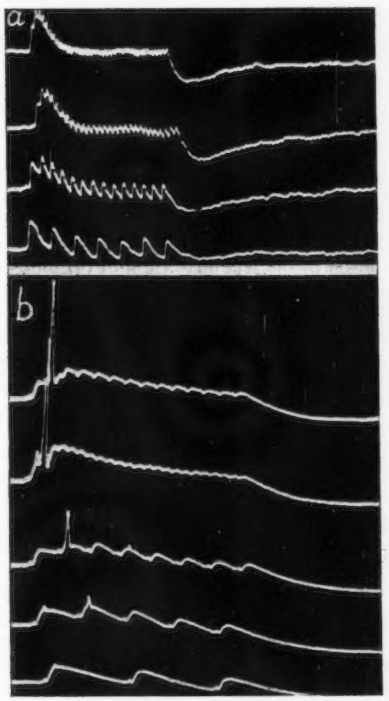

FIG. 7a. Synaptic potentials recorded from the 1st sacral ventral root and set up by repetitive orthodromic volleys in gastrocnemius nerve ; the frequencies from above downwards are 200, 150, 75 and 35 per second

FIG. 7b. As in fig. 7a, but at a lower depth of anaesthesia, so that a single orthodromic volley sets up a small reflex spike discharge and a larger spike is evoked by the second volley at high frequencies of stimulation ; the frequencies from above downwards are 350, 500, 150, 100 and 50 per second

double the single potential, and which, during continuance of the stimulation, rapidly declines to a plateau at about the level of the initial base-line (fig. 7a). On cessation of stimulation a large positive after-potential supervenes, which presumably explains the ineffectiveness of the summation. Analysis further reveals that this ineffectiveness is dependent on three factors: (i) the cumulative positive after-potentials of the preceding responses provide a positively deflected base-line on which the summed synaptic potentials are superimposed; (ii) at high frequencies the sizes of the successive synaptic potentials are greatly diminished relatively to the initial response (fig. 7a)—presumably owing to the depressant action exerted by the positive after-potential (located *ex hypothesi* in the subsynaptic membrane) on the generation of the L.R.'s by the successive C. responses of the subsynaptic membrane; (iii) at high frequencies the relatively and absolutely refractory periods both of the presynaptic fibres and of the motoneurones would also exert a depressant action.

The reflex discharges evoked during repetitive stimulation conform with the synaptic potential picture, for discharges may be evoked by the first, second and even the third volleys at high frequencies (200 up to 500 per second), but not as a rule thereafter, as would be expected from the falling level of synaptic potential at this stage (fig. 7b). A frequency as high as 75 per second is required before any summation occurs, and then it is restricted to the second volley. Since even 75 per second would be an unusually high frequency for discharges from the proprioceptors of muscle, it may be concluded that temporal summation under synaptic knobs is by itself virtually ineffective in evoking reflex discharges. As an apparent exception to the above statements, the motoneurones of some muscles give reflex discharges throughout repetitive stimulation of the large proprioceptor fibres, but there is evidence that this is attributable to additional activation through interneuronal pathways.[3]

On cessation of the repetitive train of orthodromic volleys, testing by a single similar orthodromic volley reveals a deep depression for 10 to 20 msec., resembling that following a single volley (see Section B4), and then a rapid recovery to a phase of supernormal reflex excitability (fig. 8a), which slowly decays over several minutes. Our experiments confirm the recent systematic study by Lloyd (1949) in showing that this supernormality is dependent on some change whereby a presynaptic impulse becomes a more effective excitor of motoneurones which themselves have unchanged excitability. Furthermore this change is restricted to those presynaptic fibres which were repetitively stimulated. Focal recording may reveal no change in the size of the presynaptic volley in the motor nucleus, the first sign of the supernormality being seen in the steeper rise of the synaptic potential right from its origin (fig. 8b). Lloyd (1949) suggests in explanation that the repetitive stimulation sets up a positive after-potential (P2 component) of the presynaptic fibres, which, by increasing the size of the presynaptic impulses, causes them to be more effective synaptic excitors. If such an increase were as much as 2 per cent it would be detectable in records of the presynaptic spike in the motor nucleus (fig. 8b), and yet at the same time there is an increase in the focal synaptic potential of as much as 100 per cent and a reflex spike discharge often several times the normal control. Furthermore a large facilitation

[3] Eccles & Rall, unpublished observations

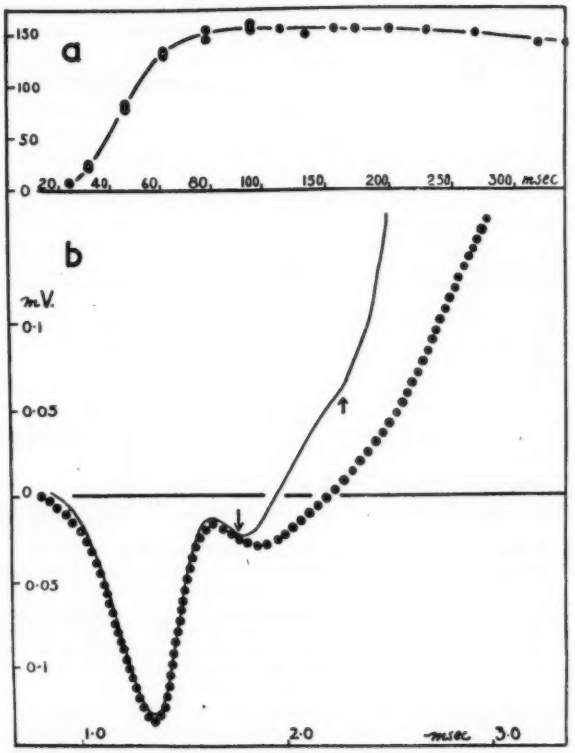

FIG. 8a. Curve drawn as in fig. 6a, but with conditioning by repetitive orthodromic volleys (300 per second for 0.17 sec.). Zero time is at last volley of conditioning series

FIG. 8b. Dotted line is the mean of six closely similar records of focal potentials set up by an orthodromic volley in quadriceps nerve and recorded just ventrolateral to the quadriceps nucleus (see fig. 5b). Continuous line shows the focal potential (mean of two closely similar records) recorded at 220 msec. after conditioning by repetitive orthodromic volleys (300 per second for 0.3 sec.). First arrow marks the first detectable sign of the increased response, which would coincide with start of the "focal synaptic potential" (cf. fig. 5c). Second arrow marks the inflection that signals the initial of the reflex spike discharge in the facilitated record (confirmed by timing of spike in ventral root, cf. fig. 5d). Note that slight difference between two records prior to first arrow is attributable to a slight shift in base-line. Stimulus to quadriceps nerve at zero of time-scale

effect, prolonged for minutes, is obtained after as few as 20 volleys, which makes the positive after-potential explanation unlikely. With the severe conditioning tetani of some thousands of volleys employed by Lloyd (1949) we have observed at long test intervals (seconds) the approximate parallelism that he reported between increased presynaptic spike and potentiated synaptic excitatory action (reflex discharge or synaptic potential). But it would appear that this correlation is merely fortuitous, because with shorter test intervals and with shorter conditioning tetani the presynaptic spike of the testing volley is diminished in size and yet there is a large potentiation of its synaptic excitatory action. It would appear that Lloyd's explanation of potentiation is inadequate.

Since it has been shown that an acetylcholine mechanism is not significantly concerned in synaptic transmission in the spinal cord (Eccles, 1947), the most probable alternative postulate is that the presynaptic impulse becomes a more effective synaptic excitor because repetitive stimulation temporarily alters the spatial relationship of the synaptic knobs to the post-synaptic membrane, e.g., the knobs may become larger and/or in closer apposition thereto. It is to be noted that this facilitation process is approximately 30,000 times longer in duration than the process due to the facilitation potential (F.P.) and thus is more likely to provide a basis for an explanation of those prolonged functional changes in the nervous system that occur in conditioned reflexes, and which presumably depend on some change in the form or structure of the synapse (Konorski, 1948).

8. Rhythmic Discharge of Motoneurones

The foregoing concepts of the excitatory properties of motoneurones may be used in outlining a hypothesis to account for the rhythmic discharges, usually at 10 to 50 per second, of motoneurones that are subjected to a continuous synaptic bombardment of sufficient intensity. The temporal summation of the excitatory effects produced by repetitive bombardment of synaptic knobs has usually been assumed to explain the build-up of an excitatory state, but it has been shown that this is ineffective at the repetitive frequencies that normally obtain (see Section B7). However, spatial summation between the excitatory effects set up under different synaptic knobs on a motoneurone is effective for the duration of the individual facilitation potential (about 15 msec.). The normal randomly distributed bombardment of the various knobs on the surface of a motoneurone is therefore likely to give rise to combinations of excitatory foci sufficiently close together in time and space to generate a propagated impulse in the way described above (see Sections B3 and B5). Following such an impulse there will be a positive after-potential and associated subnormal state (see Sections A2 and B6) from which complete recovery will take 100 msec. or more. As this recovery becomes progressively further advanced, i.e., from 20 msec. to beyond 100 msec., there is an increasing probability that the continuous random synaptic bombardment will give once more some combination of excitatory foci that will be adequate to initiate the discharge of an impulse; and so on for each successive discharge. Thus the frequency of the rhythm would be higher the more intense the bombardment; and there is in addition a random factor depending on the chance activation of contiguous knobs in close temporal sequences. The recovery from the positive after-potential would account for the fairly regular frequencies observed at any adequate intensity of bombardment; but, if the bombardment falls to such a low intensity that it rarely gives a threshold combination of excitatory foci even for the fully recovered motoneurone, the discharges will be conditioned only by the random factor and will lose all semblance of regularity. Thus the properties of motoneurones as described in the foregoing sections give a satisfactory explanation of the observed discharges of motoneurones under continuous synaptic stimulation.

ACKNOWLEDGEMENTS

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THE ROLE OF ACETYLCHOLINE IN THE CENTRAL NERVOUS SYSTEM

(149-150)

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1 Continuous activity in the central nervous system and in sympathetic ganglia
2 Acetylcholine as transmitter in sympathetic ganglia
3 Electrophysiological considerations
4 Central effects of acetylcholine
5 Central effects of eserine and other anticholinesterases
6 Mode of action of acetylcholine at the central synapse. Central depressant effects of acetylcholine and anticholinesterases
7 Release of acetylcholine
8 Changes in the acetylcholine content
9 Synthesis of acetylcholine
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It is easy to show that acetylcholine is a substance occurring naturally in the central nervous system. Properly prepared brain extracts when tested on a variety of organs show all the typical reactions of acetylcholine, and acetylcholine has, in fact, been chemically identified in brain extracts (Stedman & Stedman, 1937). The following questions then arise: is acetylcholine a central synaptic transmitter? if so, is it the universal central transmitter, or does it exert this function at certain synapses only? or is it perhaps merely a by-product of some metabolic process in brain?

The possible function of acetylcholine as a central synaptic transmitter was first envisaged by Dale (1935) and was the natural outcome of experiments which suggested that acetylcholine was responsible for neuromuscular transmission in skeletal muscle and for synaptic transmission in sympathetic ganglia.

1. Continuous Activity in the Central Nervous System and in Sympathetic Ganglia

We may, however, question the extent to which we are justified in comparing a central synapse with that in a sympathetic ganglion, where a preganglionic impulse gives rise to a single impulse in the postganglionic fibre and a 1 to 1 correspondence exists. This is in sharp contrast to the continuous activity in the central nervous system. For its explanation, the well-known theories of delayed pathways through interneurones and of re-exciting circuits in closed chains of neurones have been postulated. According to these theories continuous activity is dependent on internuncial neurones and should therefore be absent in sympathetic ganglia. But when impulses are sent into a sympathetic ganglion at a sufficiently high frequency, it continues to discharge after stimulation has come to an end (Larrabee & Bronk, 1938; Bronk, 1939; Eccles, 1944). It is true that the required frequencies are higher than any observed in vivo coming from sympathetic centres, but the results show that there is no fundamental difference between the two transmission processes. Continuous nervous activity may, in fact, depend not mainly upon the anatomical arrangement of pathways but upon some kind of ionic instability. Even nerve and muscle fibres may discharge spontaneously and "oscillate" when deprived of their calcium.

The transmission process in a sympathetic ganglion can thus still be regarded as a likely representation of what is happening at the central synapse.

2. Acetylcholine as Transmitter in Sympathetic Ganglia

Most of the evidence of the role of acetylcholine in the transmission process has been obtained on the superior cervical ganglion of the cat. This organ weighs about 20 mg. and contains, closely packed, about 100,000 cells. It can be perfused from its artery. All preganglionic fibres impinging on the cells run in the cervical sympathetic nerve, which can easily be stimulated. The theory that acetylcholine transmits the impulses from the preganglionic endings to the ganglion cells is based, in the main, on the following findings (Dale, 1914; Feldberg & Gaddum, 1934; Feldberg & Vartiainen, 1935; Brown & Feldberg, 1936a, 1936b; von Brücke, 1937; MacIntosh, 1938a, 1938b; Bronk *et al.* 1938; Bronk, 1939; Kahlson & MacIntosh, 1939; Feldberg, 1943; Sawyer & Hollingshead, 1945):

(i) Acetylcholine stimulates the ganglion cells to discharge impulses into the postganglionic fibres. The frequency of the discharge depends on the concentration of acetylcholine in the perfusion fluid. With a high concentration, stimulation is followed by paralysis. In this condition the ganglion cells no longer discharge on renewed application of acetylcholine or on stimulation of the cervical sympathetic nerve.

(ii) Acetylcholine appears in the venous effluent from a ganglion during preganglionic nerve stimulation, provided eserine is present in the perfusion fluid. The former difficulty of detecting the acetylcholine released from a ganglion perfused with whole blood has recently been cleared up by Emmelin & MacIntosh (in press). They have shown that the same amounts of acetylcholine are released per nerve impulse, whether the ganglion is perfused with eserinized saline solution or undiluted eserinized plasma. In order to obtain this result with whole blood, however, eserine had to be given in much higher concentrations, otherwise the true cholinesterase of the red cells, which is the enzyme in blood responsible for the destruction of the released acetylcholine, remains active. This had not been realized in the earlier experiments because, at that time, Mendel and Rudney's distinction between true and pseudo-cholinesterase was not known (Mendel & Rudney, 1942).

(iii) Acetylcholine is released on preganglionic nerve stimulation, even when the ganglion cells have been paralysed by curare or nicotine, but not on antidromic stimulation of the postganglionic trunk, which backfires impulses into the ganglion cells. Degeneration of the preganglionic nerve fibres entails the disappearance of acetylcholine, of choline acetylase and of true cholinesterase in a sympathetic ganglion, but its cells remain sensitive to acetylcholine. Thus, the acetylcholine metabolism in a sympathetic ganglion is located entirely in the preganglionic nerve endings. Here the

acetylcholine is stored, formed and released, and here, too, the enzyme for its destruction, the true cholinesterase, is located. The ganglion cells themselves are not involved in acetylcholine metabolism, but are merely the effector structures on which the released acetylcholine acts.

The methods used for the sympathetic ganglion are only to a limited extent applicable to the central nervous system. Synapses are not confined to one place, perfusion methods are difficult and, in addition, the transmission at the various synapses may involve different transmitter substances. Nevertheless, attempts have been made to apply the methods used on sympathetic ganglia, or modifications of these methods, to the central nervous system. We shall confine ourselves to a discussion of the results obtained by the following lines of research: the central actions of acetylcholine; the central actions of anticholinesterases; the release of acetylcholine; changes in the acetylcholine content; and synthesis of acetylcholine.

3. Electrophysiological Considerations

The problem of central synaptic transmission by acetylcholine has also been taken up by electrophysiologists, and many have stated that acetylcholine cannot be the central synaptic transmitter. They have certain ideas of how the acetylcholine released at the synapse should influence their electrical recordings, but these expected changes have not been observed. The following example, however, may illustrate the difficulty of deciding the acetylcholine theory of central synaptic transmission on electrophysiological data alone. Measurements have been made of the synaptic delay in the central nervous system and at some synapses the delay was found to be about 0.5 msec. (Lorente de Nó, 1939), an extremely short time interval indeed, so short that it appeared to exclude the possibility of release and action of acetylcholine. What it actually excluded was the possibility that a process of diffusion of a substance from the site of liberation to a distant site of action could be involved in the transmission process.

Far too much emphasis has been laid on the brevity of the time intervals as an argument in favour of or against the acetylcholine theory. These measurements give us a time limit in which the process has to occur, but they do not provide evidence of its nature. The corresponding time values for neuromuscular transmission or for synaptic transmission in a sympathetic ganglion are of the order of 2 to 3 msec. If we can imagine a process happening within 2 msec., there are no insurmountable difficulties in envisaging it happening in a quarter of that time. We should remember that the role of acetylcholine in the transmission from motor ending to motor end-plate, or from sympathetic ending to the cell of a sympathetic ganglion, was not determined electrophysiologically, and it is doubtful whether the issue of a transmission process can be decided by this approach. If other methods prove that acetylcholine has a function as a central synaptic transmitter, the electrophysiological facts must be interpreted accordingly; if proof for a different mechanism should be found, they would have to be explained in terms of this other mechanism. To use an analogy: the thermometer measures the temperature of a patient, but the finest analysis of a temperature curve is insufficient to decide which bacterium or virus is responsible for the infectious disease, though it may provide suggestive evidence.

4. Central Effects of Acetylcholine

Acetylcholine applied locally, or injected through the vertebral or carotid artery, or intrathecally, has both stimulating and depressant central effects. These are enumerated in Table I, which is not meant to give a complete list of all central effects so far found, but to illustrate the fact that the action of acetylcholine on many sections of the neuro-axis, from the cerebral cortex to the spinal cord, has been described.

In some instances, particularly when acetylcholine is applied locally, it is advisable to give eserine beforehand. For example, the local application of acetylcholine to the cortex of the cat's brain appears to produce its full characteristic effect only when this is done. Then, however, it induces large 10 per second spikes in the electrocortigram, together with motor activity on the contralateral side. The "acetylcholine spikes" suggest synchronous firing of several cortical neurones under the influence of cells with short axons, each of which controls a number of pyramidal cells (British Association, 1948). The electrical discharges of the cortex produced by acetylcholine are similar to seizure discharges, and several authors take the view that a disturbance in the acetylcholine metabolism may be an important factor in the causation or mechanism of the convulsive seizures in epilepsy (Brenner & Merritt, 1942; Forster, 1945; Richter & Crossland, 1949).

The question has often been asked whether the central actions of acetylcholine should be classed as muscarine or as nicotine actions. This classification of the peripheral actions of acetylcholine was suggested by Dale in 1914. It is not possible to extend the nomenclature to the central actions without encountering certain difficulties. If atropine sensitivity were taken as the decisive factor in classification, many of the central actions of acetylcholine would have to be grouped with the muscarine actions. But the subdivision emphasizes also the structures on which the acetylcholine acts. Its effect on gland cells, smooth muscle, heart and the capillary endothelium falls within the domain of muscarine action, whereas the nicotine action is exhibited on the cells of the suprarenal medulla, the motor end-plates of skeletal muscle and on the nerve cells of sympathetic and parasympathetic ganglia. The structures involved in muscarine action have nothing in common with the cells of the central nervous system, but the properties of the motor end-plates and of the cells of the autonomic ganglia resemble those of the cells of the central nervous system. Therefore it is probably better to associate the central actions of acetylcholine with its nicotine actions but to confine the rigorous classification of muscarine and nicotine action strictly to its peripheral effects.

5. Central Effects of Eserine and other Anticholinesterases

It may be argued that we are not justified in regarding the effects of acetylcholine as anything more than interesting pharmacological phenomena; after all, there are many substances affecting central nervous activity, often in an even more striking manner. Against this argument, we can state that acetylcholine is a substance occurring naturally in the central nervous system and that we can obtain similar effects when, instead of applying acetylcholine artificially, we create conditions in which acetylcholine released at the synapse is prevented from being destroyed and thus allowed to

TABLE I. SUMMARY OF THE CENTRAL EFFECTS OF ACETYLCHOLINE

Site	Method of application	Effects	References
Cerebral cortex (man, cat, rabbit)	Local application ; arterial and intracisternal injection	On local application : motor effects on contralateral side. On intracisternal injection : general convulsions. Typical changes in cortical electrogram. Increased amplitude and frequency of Berger waves on arterial injections of 0.1–0.2 μg. Increased electrical activity and after-discharge to stimuli in acoustic region (awakening reaction) and in area for mastication. Stimulation of suppressor areas	Sjöstrand, 1937; Bonnet & Bremer, 1937a, 1937b ; Bremer, 1938 ; Moruzzi, 1939 ; Miller, Stavraky & Woonton, 1940 ; Gerard, 1941 ; Chatfield & Dempsey, 1942 ; Brenner & Merritt, 1942 ; Forster & McCarter, 1945 ; Forster, 1945 ; British Association, 1948 ; Beckett & Gellhorn, 1948 ; Hyde, Beckett & Gellhorn, 1949
Hypothalamus	Intraventricular injections	Sleep and drowsiness obtained regularly in cats, irregularly in man Apnoea ; inhibition of motor activity of intestine	Dikshit, 1935 ; Silver & Morton, 1936 ; Henderson & Wilson, 1936 Emmelin & Jacobsohn, 1945
Supra-optic nucleus (dog)	Local application	Release of posterior pituitary hormone	Pickford, 1939, 1947
Respiratory centre	Local application. Injections with chemo-receptors excluded	Stimulation preceded or followed by depression	Dikshit, 1934 ; Heymans *et al.* 1935 ; Shuh, Wang & Lim, 1936 ; Schweitzer & Wright, 1938a, 1938b ; Gesell, Hansen & Worzniak, 1942 ; Gesell & Hansen, 1943 ; Miller, 1943
Trigonum hypoglossi	Local application	Tongue contractions. Deglutition	Miller, 1943 ; British Association, 1948
Cardiac centres	Arterial injection	Irregularities of heart action, as on central vagus stimulation	Dikshit, 1934 ; Heymans *et al.* 1935 ; Silver & Morton, 1936 ; Henderson & Wilson, 1936
Pressor centre	Iontophoresis	Rise in arterial blood-pressure	Shuh, Wang & Lim, 1936
Spinal cord	Perfusion experiments. Arterial and intrathecal injections	Discharge of motor impulses Reflex activity altered	Feldberg & Minz, 1932 ; Lefèbre & Minz, 1936 ; Bülbring & Burn, 1941 ; Calma & Wright, 1944 Schweitzer & Wright, 1937 ; Bonvallet & Minz, 1937, 1938a, 1938b ; McKail, Obrador & Wilson, 1941 ; Martini & Torda, 1938 ; Torda, 1940 ; Bülbring & Burn, 1941 ; Kremer, 1941

accumulate. Such a condition is brought about by the action of anticholinesterases.

The cardinal problem of the action of these substances is the extent to which we are justified in attributing their effects to the accumulation of undestroyed acetylcholine. If this were indeed the whole explanation of the mechanism, then the effects of anticholinesterases would represent the strongest evidence for the acetylcholine theory of central synaptic transmission. The problem is not an easy one. The cholinesterase-inhibiting action of eserine, for instance, is explained on the assumption that it competes with acetylcholine for the same receptor of the enzyme. But if they compete for the same receptor, they may also do so at the respective functional receptors of the nerve cells. Thus the possibility exists of acetylcholine-like actions of anticholinesterases independent of the inhibition of true cholinesterase. In fact, such actions do occur in the case of prostigmine. For instance, Ricker & Westcoe (1948) have recently shown that prostigmine produces muscular contractions when injected into the muscle artery of a cat whose cholinesterase has been completely inhibited by previous treatment with another anticholinesterase such as di-isopropylfluorophosphonate (DFP).

Concerning the *peripheral* actions of eserine, there are many observations which provide strong proof that they are fully accounted for by inhibition of the enzyme. The following three instances show that an acetylcholine-sensitive structure reacts to eserine only when acetylcholine is present and released.

i. The isolated intestine and uterus of the guinea-pig : both contract to acetylcholine, but the intestine alone to eserine. The intestinal wall produces and releases acetylcholine continuously ; this is not true of the uterus.

ii. Acetylcholine and eserine both constrict the pupil. But after degeneration of the parasympathetic nerve supply, the pupil no longer contracts to eserine, whereas it still contracts to acetylcholine. The normal iris contains acetylcholine ;

the denervated iris is free from it. Thus, eserine cannot act.

iii. Eserine injected into an anaesthetized cat causes fascicular twitchings and fibrillation of skeletal muscles even after severance of the motor nerves, but two to three days after nerve section eserine is inactive. Within this time the nerve fibre and its ending have lost their acetylcholine, their ability to form it and consequently to release it. Thus eserine has become inactive. This instance is of particular interest because the processes at the motor end-plate have always been regarded as furnishing a kind of analogy to those at the central synapse.

If the peripheral actions of eserine can be accounted for by accumulation of released acetylcholine, the same mode of action may apply at least to some of the central actions of eserine. This appears to be the only convincing explanation of the effects of small doses of eserine. Larger doses, however, may have additional " direct " effects as well. In particular, the paralysing effects so easily obtained with larger doses of eserine and of other anticholinesterases may not always be due solely to accumulation of acetylcholine. Some ideas about this paralysing action will be given later.

There is no need to enumerate the central actions of eserine and other anticholinesterases. They resemble those of acetylcholine with the following main differences : (i) the onset and the disappearance of the effect is usually more gradual than with acetylcholine and (ii) compared with acetylcholine, depression is even more pronounced and more easily obtained than stimulation.

From among the great number of observations which show that eserine causes discharge of motor impulses in the central nervous system, followed by depression, I would like to mention one observation on the isolated cat's head perfused with diluted blood (Chute, Feldberg & Smyth, 1940). This observation was not the first, nor even an important one, but it is particularly impressive. The fully isolated head was mounted on a stand and connected with the perfusion arrangement by rubber tubing. On the addition of eserine to the perfusion fluid, there occurred a spontaneous blinking reflex at a rate of about 80 per minute and jerky movements of the head. A striking picture indeed ! The muscular contractions were of central origin and disappeared after motor nerve section. How can they be explained if not by accumulation of released acetylcholine ; and, if this is so, then—at least for some of the synapses involved in the central pathways of these reflexes—acetylcholine must be the central transmitter.

Schweitzer, Stedman & Wright (1939) have tried to explain the variety of effects obtained with various anticholinesterases. Tertiary bases such as eserine are lipid-soluble and were thought to penetrate the cells and act as convulsants, whereas quaternary bases, such as prostigmine, are lipid-insoluble and were thought to remain outside the cells and act as depressants. This theory, attractive as it may appear, does not, however, explain all the known facts ; there are sufficient observations, such as those by Merlis & Lawson (1939) McKail, Obrador & Wilson (1941), Bülbring & Burn (1941) and Calma (1949), which show that eserine and prostigmine influence reflex activity in the same way.

Recently, another anticholinesterase, DFP, has been widely examined. Its anticholinesterase activity was discovered during the war, independently by Adrian, Feldberg & Kilby (1947) and by Mackworth & Webb (1948). It differs from eserine in its much more prolonged action, which is due to the fact that it forms an irreversible combination with the enzyme. Another recently discovered inhibitor of cholinesterases (DuBois & Mangun, 1947), probably acting like DFP, is tetraethylpyrophosphate (TEP). But both substances also inhibit respiration of brain tissue and, in this respect, differ from eserine. Some of their depressant actions may therefore result not from inhibition of cholinesterase but from interference with the cell metabolism (Brooks, Ransmeier & Gerard, 1949).

When DFP was given to human patients over long periods, they complained of disturbed sleep and nightmares (Grob *et al.* 1947 ; Rowntree, Nevin & Wilson, 1950). In this connexion it is interesting to note that, in one of the first papers written on the pharmacological action of eserine, in 1876, Harnack & Witkowski describe how eserine injected into an epileptic idiot caused convulsions and, in addition, the idiot behaved as if he had had hallucinations. It is interesting to speculate, although we cannot do more at present, if these effects are the results of inhibition of cholinesterase and are brought about by accumulation of acetylcholine on the sensory side of the brain.

Duke, Pickford & Watt (1950) injected small amounts of DFP into the region of the supra-optic nucleus in dogs, and observed a profound and long-lasting inhibition of the rate of urine flow, followed by a diabetes insipidus lasting for a few weeks. We have seen that an injection of acetylcholine into this region causes the release of the antidiuretic hormone, and the delayed effect of DFP could be explained by its paralysing action. The acetylcholine released by cholinergic nerve endings impinging on the supra-optic nucleus would no longer be destroyed and, by its persistence, would give rise to the paralysing action. But we cannot discard the alternative explanation that paralysis is due to direct interference with the cell metabolism.

6. Mode of Action of Acetylcholine at the Central Synapse. Central Depressant Effects of Acetylcholine and Anticholinesterases

We may form an idea of how acetylcholine acts on the central nervous system from an analogy with its effect on motor end-plates of striated muscles or on cells of sympathetic ganglia. Acetylcholine depolarizes these structures. The depolarization can be recorded and is known as the motor end-plate potential (Göpfert & Schaefer, 1937 ; Schaefer & Haass, 1939 ; Eccles & O'Connor, 1939 ; Eccles & Kuffler, 1941 ; Eccles, Katz & Kuffler, 1941a, 1941b, 1942 ; Kuffler, 1943). Depolarization of the ganglion on preganglionic nerve stimulation has been recorded by Eccles (1943, 1944) and termed " synaptic potential " ; a better name would be " ganglion potential ". These potentials then give rise to the impulse or excitation wave along the fibre of the postganglionic nerve or muscle. Evidence in support of this view has been obtained from quite a different source (Beutner & Barnes, 1941, 1942). A model of a polarized surface with a lipoid layer in contact with saline solution can be connected to an amplifier by leads applied to the two surfaces of the interface. A positive electromotive force may then be recorded. This quickly declines when minute amounts of acetylcholine are added to the saline solution.

Probably acetylcholine also depolarizes some surface of the nerve cell in the central nervous system and this depolarization then provides the appropriate stimulus for initiating the nerve impulse in the axon. This view enables us to understand why

stimulation is so often followed by depression, and why the latter is often observed more easily than stimulation. When acetylcholine acts as the physiological stimulus at central synapses, it is destroyed by the true cholinesterase the moment the acetylcholine is released; the surface thus becomes repolarized and ready for depolarization by a renewed charge of acetylcholine. With most of the methods of artificial application of acetylcholine, however, depolarization will persist for some time, because the large amounts of acetylcholine are no longer dealt with quickly enough by the normal protective mechanism of enzymatic destruction; in addition, depolarization will no longer be restricted to those relevant points where the nerve endings impinge on the cell; on the contrary, the whole cell may be "flooded" with acetylcholine. In order to understand how this can cause depression we may follow Sherrington's earlier suggestion and look upon transmission at the motor end-plates as furnishing a pattern or paradigm of what happens at the central synapse.

Acetylcholine may cause either contraction, depression or contracture of the skeletal muscle and all three effects can be explained by the depolarizing action of acetylcholine.

When released from the motor nerve-ending under physiological conditions, the only region which becomes depolarized by the acetylcholine is the motor end-plate. This depolarization furnishes the appropriate stimulus for the excitation wave along the muscle fibre and its subsequent contraction. This action of acetylcholine is represented diagrammatically in fig. 1a. But when a large dose of acetylcholine is injected into a muscle artery, contraction is often followed by depression. The same occurs with smaller doses of acetylcholine when its destruction is prevented by eserine or another anticholinesterase, as shown in fig. 2. Depression is seen also when the nerve to the muscle is frequently stimulated in the presence of eserine. Figures 2 and 3 illustrate the fact that eserine has two actions on the muscle contraction elicited by nerve stimulation; it potentiates the single twitch, but depresses the

FIG. 1

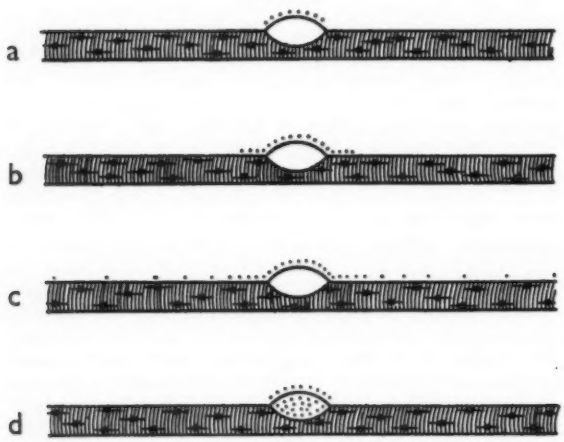

Fig. 1. Diagram of four skeletal muscle fibres with their end-plates, to illustrate the actions of acetylcholine. Depolarization shown by dots

a : the physiological stimulating action

b, c, d : three possible forms of the paralysing action (For details, see text)

FIG. 2

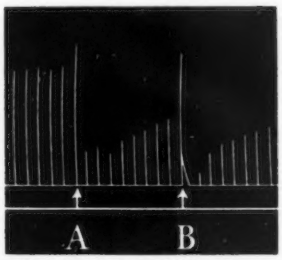

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Fig. 2. Spinal cat.

Contractions of gastrocnemius muscle in response to single maximal shocks to nerve at 10 sec. intervals, after arterial injection of 0.1 mg. of the anticholinesterase miotine

A : arterial injection of 10 μg. acetylcholine

B : short tetanic stimulation of nerve

tetanus. The depression of the muscle responses is explained either by prolonged persistence of acetylcholine at the end-plate region or, more likely, by depolarization extending beyond this region to the muscle fibre. In the diagrammatic representation (fig. 1), depolarization beyond the end-plate region is indicated in b and c. It makes no difference for the purpose of interpretation whether this depolarization affects only a small region beyond the end-plate or the whole muscle fibre. In both conditions depression would result, because depolarization of the fibre, unlike that of the end-plate, does not give rise to an excitation wave but, on the contrary, forms an inexcitable region which blocks transmission. Thus, even depolarization of a minute part of the muscle fibre adjacent to the end-plate acts as a block, and would fully explain the phenomenon of the depressant action. Two facts support the view that, during the condition of acetylcholine depression, parts at least of the muscle fibre are depolarized: first, the finding that the reduced excitability applies not only to nerve stimulation but also, although to a lesser degree, to direct muscle stimulation (Brown, Dale & Feldberg, 1936); and second, the acetylcholine contracture. This phenomenon has not been sufficiently considered in the interpretation of the mode of action of acetylcholine. By a contracture we mean a form of contraction which develops more slowly than a twitch or tetanus; tension is not as high as that of a summated contraction; heat and lactic acid are produced; and that part of the muscle which is in a state of contracture becomes negative to the resting part, i.e., it is depolarized. Where it differs from the picture of normal contraction is in the conduction of the mechanical response and the propagation of excitation. In the state of contracture the muscle fibre is depolarized and electrically inexcitable; the contracture thus prevents propagation along the muscle fibre of excitation waves arising from the motor end-plate. This accounts for the depression of the response to nerve stimuli, a characteristic of muscles in contracture. When the contracture is localized in a muscle fibre it forms a region of neuromuscular block. Contractures and depression of response are therefore both signs of a depolarization of the muscle fibres.

FIG. 3

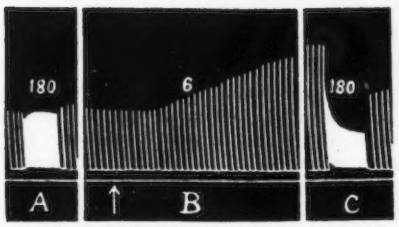

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Fig. 3. Cat, under chloralose anaesthesia

Contractions of tibialis anticus in response to maximal shocks to nerve at frequency of either 6 or 180 per min. At arrow, intravenous eserine 0.5 mg. per kg. bodyweight. The white patches are caused by overlapping of the individual contractions during high frequency stimulation

In denervated mammalian muscle, as well as in normal avian or amphibian muscle, acetylcholine causes typical contractures; in other words, depolarization of the muscle fibre beyond the end-plate region occurs. Similarly, Feng & Shen (1937) have shown that, for frog muscle, repeated nerve stimulation after eserine leads to a contracture restricted to the region near the end-plate, i.e. there is again depolarization beyond the plate region.

There is thus sufficient evidence to show that acetylcholine depolarizes at least part of the muscle fibre and that the depressant action is thereby explained. Nevertheless, prolonged persistence of acetylcholine at the end-plate region might itself produce depression. On this assumption, the persistence of acetylcholine would result in a derangement of the finely adjusted mechanism of depolarization and repolarization, which apparently is required for the proper functioning of the end-plate region. The condition is represented diagrammatically in fig. 1d. The phenomenon of depression can certainly be obtained in the absence of any muscle fibres as, for instance, in the electric organ of the torpedo fish. This organ consists of exaggerated electric plates, which are modified motor end-plates lacking the contractile fibre. The release of acetylcholine by the nerve impulse leads to depolarization of the ventral surfaces of the plates, which are quickly repolarized when the acetylcholine is destroyed by the true cholinesterase (Feldberg & Fessard, 1942). After eserine, however, the effect of repeated nerve stimulation becomes more and more reduced and may disappear. This " depression " is explained either by continued depolarization of the ventral surface of the plates, or by the fact that the released acetylcholine " floods " parts of the plate, perhaps even the dorsal surface which is normally not reached by the acetylcholine. The sequence of events at the electric organ thus provides no proof for the view that prolonged persistence of acetylcholine at the points of its physiological action is sufficient to produce a condition of depression.

The depressant actions of acetylcholine and anticholinesterases on the central synapses may be explained in a similar fashion; prolonged depolarization or " poisoning " by acetylcholine of parts normally depolarized for an extremely short period, or depolarization of regions of the cell which are normally not reached by the released acetylcholine and which may even extend to the beginning of the axon, may account for the depression. We can now understand not only why the depressant actions are so prevalent with anticholinesterases but also why stimulant effects are so much more difficult to obtain than in skeletal muscle. In the latter, only the response to single nerve impulses is potentiated by eserine; the tetanic contraction obtained with repeated nerve stimulation is depressed, as seen in fig. 3. The continuous activity in the central nervous system, however, resembles not the single impulse but the repeated stimulation. It is thus not surprising that the anticholinesterases are central depressants; what is surprising is that they often exert central excitatory effects.

The central depressant actions of acetylcholine, and of anticholinesterases like eserine, thus present strong evidence for the acetylcholine theory of central synaptic transmission. This has not always been fully recognized.

The above considerations do not necessarily apply to the effects obtained with high concentrations of DFP, TEP or even of eserine. In these conditions we may be dealing, in part at least, with direct depressant actions not accounted for, or not wholly accounted for, by released acetylcholine.

7. Release of Acetylcholine

The release of acetylcholine on stimulation of the nerve has always provided the first and most important part of the evidence for the cholinergic nature of a peripheral nerve. The method has not had a wide application in the central nervous system. This is not surprising when we consider the difficulties inherent in perfusion experiments of this part of the body. But the few results so far obtained (for references see Feldberg, 1945b) support the acetylcholine theory of central synaptic transmission.

The central nervous system exhibits continuous activity; therefore acetylcholine should be released continuously in the absence of special external stimuli. It has, in fact, been found by all workers on this subject, that after eserine, acetylcholine appears " spontaneously " in the cerebrospinal fluid as well as in the venous effluent from the central system. In certain conditions, this spontaneous output increases, as for instance after central vagus stimulation, or stimulation of the sinus nerve, after asphyxia and, strangely enough, after administration of adrenaline. By far the most convincing evidence regarding increased release of acetylcholine as a result of increased central activity is given by Bülbring & Burn (1941). They perfused the lower half of the spinal cord of dogs with eserinized saline solution. Reflex activity persisted for eight minutes; during this period they stimulated the central end of the cut sciatic nerve and obtained an increased output of acetylcholine in the venous effluent. Figure 4, taken from their paper, shows the effect of effluent, collected before and during stimulation, on leech muscle.

8. Changes in the Acetylcholine Content

The problem of the acetylcholine content of the central nervous system has to take into account the following facts: (i) acetylcholine is present in the tissues in a bound form in which it is inactive and protected against enzymatic destruction; (ii) as soon as it is set free it is at once destroyed by true cholinesterase; (iii) the released acetylcholine is rapidly replaced by synthesis, the new acetylcholine being synthesized in the bound form.

FIG. 4

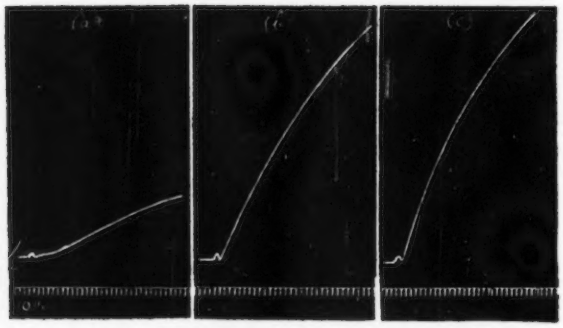

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Fig. 4. Leech muscle

a : effect of a control sample of venous effluent from spinal cord taken 3 min. after Ringer perfusion was started

b : contraction produced by a sample collected after 2 min. stimulation of the central end of the sciatic nerve

c : contraction produced by acetylcholine (1 in 50 million)

If destruction of the released acetylcholine and its replacement by synthesis were to proceed at the same rate, variations in the functional activity of the brain would produce no change in the acetylcholine content—even if these variations were associated with increased and decreased release of acetylcholine. The acetylcholine content of a given part of the central nervous system would have a constant value, determined probably by the number of available tissue constituents to which acetylcholine is bound. This view is correct to a limited extent only.

Most of the earlier experiments (for references see Feldberg, 1945b) which dealt with variations in the acetylcholine content of the central nervous system were undertaken without taking into consideration or making allowance for the fact that release, destruction and synthesis of acetylcholine take place very rapidly. It is therefore not surprising that the results were contradictory and anything but convincing.

However, recent experiments on rats carried out in the Neuropsychiatric Research Centre in Cardiff have shown that, if brain tissue is rapidly fixed, the level of its acetylcholine content shows variations dependent on the state of functional activity of the brain prevailing during the time of fixation (Richter & Crossland, 1949). Replacement by synthesis apparently does not keep pace with the release and destruction of acetylcholine.

In the experiments of Richter & Crossland the method of rapid fixation was that formerly used by von Muralt (1937) on peripheral nerves ; i.e., the animals were killed by immersion in liquid air. The brains of rats killed during anaesthesia or sleep showed an increased acetylcholine content, those killed in emotional excitement or convulsions a decreased acetylcholine content. The changes were large but transient. The values for the convulsed animal were only 25–30% of those obtained in anaesthesia ; when the animals were killed only a few seconds after electrically induced convulsions, the acetylcholine level had returned to its normal level. Even with the method of immersion in liquid air it took approximately 4 sec. for the brain to cool to 0° C. ; with quicker methods of fixation, still greater variations in the acetylcholine content might have been obtained.

9. Synthesis of Acetylcholine

There are different methods available for studying the synthesis of acetylcholine. When we incubate tissue slices or minced tissue, the enzyme is not in solution ; the synthesis occurs in the slices or cell debris, and the acetylcholine is released from them and diffuses into the solution (Mann, Tennenbaum & Quastel, 1938, 1939). The method actually does not distinguish between synthesis and release. Glucose must be present in the incubation medium when this method is used, but the concentration necessary for optimal synthesis is only about 10% of that existing in blood. The normal concentration in the blood actually depresses synthesis or release.

If similar conditions prevail in the body, it means that the blood-glucose exerts normally a restraining effect on the continuous synthesis or release of acetylcholine in the central nervous system. Lowering the blood-glucose would remove the " glucose brake " and allow synthesis and release to proceed at an abnormal rate. The result would be the same as if acetylcholine had been applied to the motor cortex, i.e., convulsions would occur. Insulin convulsions might thus be explained on the acetylcholine theory of central synaptic transmission (Feldberg, 1945a, 1945b).

The hunger contractions of the stomach associated with a lowering of the blood-glucose might be interpreted as being due to a similar mechanism, i.e., removal of the glucose brake—partly in the stomach wall but mainly in the central nervous system—on the acetylcholine release, and synthesis at the nerve endings impinging on the vagal centres or at neurones situated higher up in the neural axis.

A great advance was made when it became possible to bring the enzyme for synthesis of acetylcholine into solution. This we owe to Nachmansohn & Machado (1943). They showed that the enzyme acts by acetylation of choline and that adenosinetriphosphate is necessary for the reaction. They termed the enzyme : choline acetylase. The experiments were performed on homogenized brain ; later Feldberg & Mann (1944, 1945) used extracts from acetone-dried brain. The biochemical reactions involved in the synthesis are rather complicated and not yet fully understood (for references see Feldberg, 1950). For optimal synthesis of acetylcholine to take place in saline extracts prepared from acetone-dried brain, the following substances have to be added to the incubation medium : choline, adenosinetriphosphate, magnesium, potassium, cysteine, citrate, and activator or coenzyme A. Eserine and sodium fluoride are added as well, as a precaution, in case traces of cholinesterase or phosphatase are still present in the extract. Cysteine is necessary in aerobic conditions in order to keep the SH groups of the enzyme reduced and active. The action of citrate is not clear ; it may act as a source of acetate. The activator or coenzyme A is a heat-stable, dialyzable substance present in extracts of brain and of many other tissues. According to Lipmann *et al.* (1947), it is a derivative of pantothenic acid ; it appears to be the co-enzyme for acetylation in general and not for choline alone.

The great advantage of the use of acetone-dried tissue is that the amount of tissue required is small, so that determinations can be made with a few milligrams of tissue. Making

FIG. 5

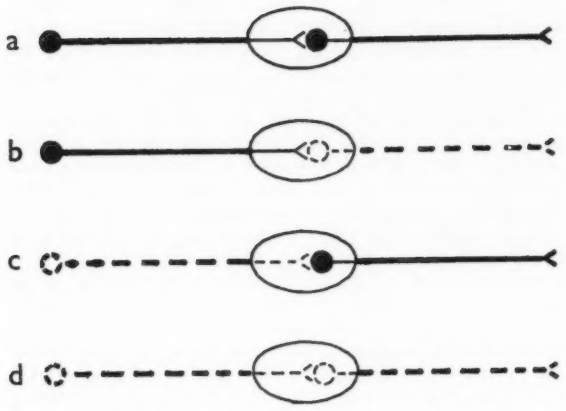

Fig. 5. Four possible arrangements (**a, b, c, d**) of cholinergic and non-cholinergic neurones at the synapse

cholinergic

non-cholinergic

use of this fact, the synthesis of acetylcholine has been studied in various relatively well-defined areas of the central nervous system with the idea of mapping out the distribution of the enzyme, and on the assumption that acetylcholine is perhaps not the universal central synaptic transmitter, but that the central nervous system is built up of cholinergic and non-cholinergic neurones (Feldberg & Vogt, 1948). So far, these experiments have been confined to dogs. The acetylcholine-synthesizing power of a number of regions and tracts of the central nervous system was studied, but the results obtained seemed at first sight confusing. High and low values occurred in regions belonging to the same efferent or afferent pathway. However, by applying our knowledge of the properties of cholinergic neurones in the peripheral nervous system to the results, some interpretation became possible.

Assuming there are two kinds of neurones, then four connexions are possible at the synapse, as indicated in fig. 5, and the following conclusions and approaches appear justified :

i. A cholinergic neurone is characterized by the fact that it synthesizes acetylcholine not only at its ending but along the whole course of its axon. Thus, a tract composed of cholinergic fibres will be identified by a high concentration of choline acetylase.

ii. On the other hand, a bundle of non-cholinergic fibres will be identified by the nearly complete absence of choline acetylase.

iii. Since the enzyme is apparently located in the axon and not in the myelin sheath, the thickness of the latter may affect the result. Thus, an intermediate value may not necessarily mean a mixture of cholinergic and non-cholinergic neurones. This introduces a difficulty, and interpretation depends largely on those less frequent regions with either high or low values.

iv. Concerning the grey matter, we must realize that the greyness is not so much determined by the nerve cell as by the abundance of non-myelinated fibres. The myelin sheath does not start at the very beginning of an axon, nor extend right to the end, as indicated diagrammatically in fig. 5. A high value for synthesis of acetylcholine may thus indicate one of three possibilities : (i) the neurones of which the nerve cells form a part are cholinergic ; (ii) only the fibres terminating at these cells are cholinergic ; (iii) both are cholinergic. Therefore, a high concentration of enzyme in a region of grey matter does not necessarily imply that the enzyme is produced by the cell body or its axon. In the peripheral nervous system this fact is illustrated by the sympathetic ganglia, which contain cells of non-cholinergic neurones. More information can, therefore, be obtained if, in addition to the synthesizing power of the region of a nucleus, that of the tracts passing to and from the nucleus is known as well.

v. Occasionally, use can be made of our knowledge of the central actions of acetylcholine in the interpretation of the results. It is necessary to emphasize that the sensitivity of a nerve cell does not depend on whether or not it gives rise to a cholinergic axon ; for instance, the sympathetic ganglion cells, which are the cell bodies of adrenergic neurones, are sensitive to acetylcholine. The reverse conclusion—that cells which respond to acetylcholine are cells upon which cholinergic neurones impinge—is more likely to be generally true.

With these facts in mind, an interpretation was attempted and it was found that often, although by no means always, the arrangement of neurones in the efferent and afferent nervous pathways was such that cholinergic and non-cholinergic neurones alternated with each other. For example, in the voluntary motor pathway, the finding of a high choline acetylase concentration in the anterior horns, in the motor nuclei of the cranial nerves and in the anterior roots suggests the cholinergic nature of the lower motor neurone. On the other hand, low values were encountered in the pyramidal tracts, indicating that the upper motor neurone is non-cholinergic. The fibres of the pyramidal tracts are not the only ones to impinge on the anterior horn cells. Fibres from other systems, some of which may be cholinergic, terminate at these cells. The same cell may, therefore, be impinged upon by cholinergic and non-cholinergic fibres. In the motor area of the cerebral cortex an intermediate value was found, which might suggest that cholinergic neurones converge on the pyramidal cells. This suggestion is strengthened by the fact mentioned earlier that both eserine and acetylcholine, when locally applied to the motor cortex, initiate impulses in the pyramidal tracts.

Evidence for a succession of alternating non-cholinergic and cholinergic neurones is also found in afferent pathways. Low values found for the posterior roots and their central continuation, the funiculi gracilis and cuneatus, are in agreement with the conception that the first neurone of the afferent sensory pathway is non-cholinergic. However, relatively high values were obtained for the nuclear masses in which these sensory fibres end ; this was taken to indicate the cholinergic nature of the second neurone in the sensory pathway. More recently, in 1949, Feldberg, Harris and Lin examined tracts of secondary sensory neurones (unpublished work). Whereas the eighth cranial nerve itself lacked the enzyme, the trapezoid bodies and the lateral filament which contain the fibres of the second ascending neurone gave intermediate values. Similarly, the region of the spinal cord which contains, amongst other fibres, those from the spino-cerebellar tract, i.e., of the second ascending neurone, also gave intermediate values. The third sensory neurone, originating in the thalamus and leading to the cortex, is probably again non-cholinergic, as suggested by

the low values found for the fibres in the posterior part of the internal capsule which, at least in man, is said to contain the thalamic radiation.

Another example is provided by the optic pathway. The retina contains large amounts of choline acetylase, whereas the optic nerve is free from it. This suggests that acetylcholine is the chemical transmitter at one or more of the synaptic junctions in the retina, but that the optic nerve is non-cholinergic. Observations made in 1949 on *Sepia* by Feldberg, Harris and Lin (unpublished work) suggest that, in the squid at least, the first neurone originating in the retina is also non-cholinergic. In *Sepia*, the retina consists of one kind of visual element only, which may correspond to the rods, and the nerve fibres originating from these pass, without synaptic interruption, as retinal nerves out of the eye and into the optic ganglion. It was found that in *Sepia*, the retina and the retinal nerves lack choline acetylase, which is highly concentrated in the optic ganglion. It is tempting, but dangerous, to use these results for interpretation of results obtained on the mammalian retina. But it may well be that the high concentration of choline acetylase in the mammalian retina is solely accounted for by the presence of the short second neurones. In that case, the first neurone originating in the rods and cones would be non-cholinergic and the second neurone cholinergic. This neurone then impinges in the ganglionic layer on the cell bodies of the non-cholinergic third neurone, the optic nerve. The fourth neurone in the optic pathway may again be cholinergic, as indicated by the high values found for the lateral geniculate bodies, where this fourth neurone begins.

Very low values for choline acetylase were found in the tissue of the anterior and posterior pituitary gland, but the region of the supra-optic nucleus gave a high value. This suggests that the last neurone by which nerve impulses are conveyed to the posterior pituitary is non-cholinergic, but that the fibres impinging on the supra-optic nucleus are cholinergic; the fact that the cells of this nucleus are sensitive to acetylcholine (Pickford, 1947) is in agreement with this concept.

However attractive such a pattern of a succession of alternating non-cholinergic and cholinergic neurones may be, it would be dangerous to have a conception which is too simplified and diagrammatic. We must realize that, if there are two different kinds of neurones, then on purely statistical grounds there must be considerable alternation.

About the nature of the non-cholinergic neurones nothing definite is known. As Sir Henry Dale said at the 1948 meeting of the British Association: " It is difficult to suppose that synapses in the central nervous system can differ among themselves so fundamentally in function, that transmission at some should be cholinergic and at others involve no kind of chemical agent." (British Association, 1948).

Naturally one thinks of the transmitter for adrenergic nerves in the peripheral nervous system: adrenaline or noradrenaline. Another substance has recently been suggested by Hellauer & Umrath (1948). According to their results, the transmitter is an unknown vasodilator substance which is also responsible for antidromic vasodilatation, a possibility which had already been foreseen by Dale (1935). Destruction of this transmitter is thought to be an enzymatic process which can be prevented by strychnine in the same way as eserine inhibits cholinesterase. Strychnine convulsions would thus be explained; confirmation of these results is essential before it is possible to speculate on these startling results. Holton and Perry (personal communication, 1950), for instance, have recently shown that strychnine has no detectable effect on antidromic vasodilatation produced in the external ear of the rabbit.

Summarizing, it may be said that whatever conclusion we draw from each single finding, it is impossible to deny the fact that there is a great number of observations which can be accounted for convincingly and satisfactorily only by the acetylcholine theory, even if we agree that acetylcholine is probably not the universal central synaptic transmitter.

I find it difficult to understand the position taken up by several authors who discard all findings in favour of the acetylcholine theory as being irrelevant, but perhaps my difficulty is the result of bias and prejudice.

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CONDUCTION OF THE NERVOUS IMPULSE: SOME RECENT EXPERIMENTS

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1 Experiments with internal electrodes
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The centenary of the discovery of the action current by Du Bois-Reymond and Matteucci[1] has passed almost unnoticed by the majority of physiologists and biophysicists. But formal recognition of this event is hardly necessary, for the discovery forms the basis of most modern work on the nervous system and its importance is as clear today as it was a hundred years ago. For a long time progress was limited by the lack of suitable recording instruments, and precise information could be obtained only by the use of ingenious but indirect methods such as those employed by Bernstein (1868) or Lucas (1912).

In recent times the development of valve amplifiers and cathode-ray tubes has provided an almost perfect method of measuring rapid electrical changes. With these instruments, an observer can be sure that the electrical variations which reach his recording system are reproduced without appreciable distortion. But this is not by any means the end of the story, for it does not follow that the changes at the recording electrodes are the same as those at the active surface of a nerve or muscle fibre. Excitable cells are always surrounded by a certain amount of external fluid and the potential difference observed with external electrodes depends to a large extent upon the shunt provided by the external fluid. Another complication is introduced by the interesting phenomenon of dispersion. A mixed nerve trunk consists of many thousands of nerve fibres with diameters varying over a wide range. The conduction velocity of a nerve fibre increases with its diameter so that the action potential of a mixed nerve trunk is a compound wave which is built up from the asynchronous activity of large numbers of different fibres (Erlanger & Gasser, 1937). It is therefore a matter of some difficulty to make quantitative deductions about the behaviour of a single nerve fibre from observations with large nerve trunks. Errors may also be introduced by irregularities in the nerve trunk or by the presence of an external connective-tissue sheath. The position can be improved by using an isolated nerve fibre, but it is still necessary to allow for the shunting effect of the external fluid and this can be done only by making complicated electrical measurements.

[1] According to Biedermann (1896) the discovery was made independently by Du Bois-Reymond and Matteucci between the years 1840 and 1843. Full references to the literature of this period are given in Du Bois-Reymond's *Untersuchungen über thierische Elektricität* (1848).

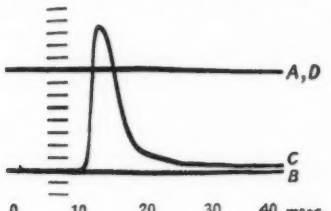
1. Experiments with Internal Electrodes

The most satisfactory method of determining the absolute magnitude of the action potential depends upon the use of an internal electrode which measures the potential difference across the cell surface. This technique has been used to measure the resting potential and action potential in the giant axon of the squid (Curtis & Cole, 1940, 1942; Hodgkin & Huxley, 1939, 1945). The methods employed by American and British investigators differ in certain minor respects, but the general principle is the same. A micro-electrode consisting of a long glass capillary is inserted at one end of the fibre and is pushed in for a distance of 10–30 mm. During this process it is important to keep the micro-electrode in the centre of the axon. If the electrode scrapes against the surface membrane it damages the fibre and the experiment is at an end; but if kept in the centre it appears to do no harm and the axon remains excitable for many hours.

The small size of most nerve and muscle fibres makes it difficult to use the technique employed for the giant axon, but another method has now been developed by a group of physiologists in Chicago (Graham & Gerard, 1946; Ling, 1948; Ling & Gerard, 1949a, b, c, d). These workers showed that a very small electrode can be inserted transversely into a muscle fibre without causing appreciable damage or twitching. The surface membrane appears to form an effective seal round the electrode, provided that the dimensions of the latter are sufficiently small. In order to obtain successful results it is desirable that electrodes should have an external tip diameter of not more than 0.5 μ. This small diameter means that the electrodes have a high electrical resistance and special precautions must be taken with the recording system. Gerard and his collaborators were primarily interested in the resting potential and made no direct measurements of the action potential. Further developments in technique have made it possible to record both action potential and resting potential with this type of electrode (Hodgkin & Nastuk, 1949; Nastuk & Hodgkin, 1949, 1950). Other investigators are now extending the method to different preparations (e.g. Coraboeuf & Weidmann, 1949) and it may prove to be an important way of investigating cells and tissues which are not amenable to more conventional methods of attack.

Two general conclusions may be drawn from the experiments with internal electrodes. In the first place, it is clear that both action potential and resting potential are developed across a thin membrane at the surface of the fibre. There was already much evidence for this conclusion, but the experiments with internal electrodes put it on a firmer basis. In this respect modern work substantiates the assumptions made in the classical form of the membrane theory, but in another respect it comes into sharp conflict with the predictions of the theory. For it is found that activity does not consist of a simple membrane break-down, but involves a substantial reversal of the membrane potential. Thus the resting potential of squid nerve is about 50 mV., while the action potential may be 100 mV. or more (Curtis & Cole, 1942;

FIG. 1. RESTING POTENTIAL AND ACTION POTENTIAL OF FROG MUSCLE FIBRE



(From Nastuk & Hodgkin (1950), by permission of the Editors of the Journal of Cellular and Comparative Physiology)

Temperature 6° C.
Ordinate scale : 10 mV. steps (from voltage calibrator)

Record A : obtained at beginning of experiment, with micro-electrode outside fibre

Record B : obtained in the resting condition, with micro-electrode inside fibre

Record C : obtained in stimulated condition, with micro-electrode inside fibre

Record D : obtained at end of experiment, with micro-electrode outside fibre

Hodgkin & Huxley, 1945; Hodgkin & Katz, 1949). The average resting potential in frog's muscle is about 90 mV., while the action potential is about 120 mV. (Hodgkin & Nastuk, 1949). A typical record which illustrates the reversal of potential difference in frog muscle is shown in fig. 1. There is evidence for a similar reversal in crustacean nerve (Hodgkin & Huxley, 1945) and it appears to be a fairly general property of excitable cells. Recent experiments suggest that the effect may have an interesting explanation in terms of permeability and ionic concentrations.

2. The Basis of the Action Potential : a Hypothesis

Table I gives approximate figures for the ionic concentrations in the interior of a frog's muscle fibre and in the surrounding Ringer's fluid. The figures illustrate the well-known result that inside the cell potassium is present in high concentrations, while sodium and chloride are present in low concentrations. We shall assume that the resting membrane is permeable to potassium and to chloride but is sparingly permeable to sodium and to the internal anions (cf. Boyle & Conway, 1941). Under these conditions a potential difference of the same sign and order of magnitude as the resting potential is to be expected. Owing to the direction of the concentration gradients, potassium ions tend to leave and chloride ions to enter the fibre. In this way a potential difference is built up which opposes further motion of ions. If the membrane were permeable to potassium ions alone we should have :

TABLE I. APPROXIMATE IONIC CONCENTRATIONS IN FROG MUSCLE

Myoplasm		Ringer's Fluid
$(K)_i = 125$		$(K)_o = 2.5$
$(Cl)_i = 1\text{–}5$		$(Cl)_o = 117$
$(Na)_i = 15$		$(Na)_o = 117$
Internal Anions = 135		
	Membrane	

Concentrations are given in milliequivalents per litre and are based on information provided by Boyle & Conway (1941). The figures given for Ringer's fluid are those used in the experiment illustrated by fig. 1 (see Nastuk & Hodgkin, 1950).

$$E_K = 58 \text{ mV. } \log_{10} \frac{(K)_i}{(K)_o} \qquad (1)$$

where E_K is the equilibrium potential for potassium; $(K)_i$ and $(K)_o$ are activities inside and outside the fibre. On the assumption that the activity coefficient inside the fibre is the same as that outside we find $E'_K = 99$ mV. for the system considered in Table I. If the membrane were permeable to chloride ions alone we should have :

$$E_{Cl} = 58 \text{ mV. } \log_{10} \frac{(Cl)_o}{(Cl)_i} \qquad (2)$$

$$E'_{Cl} = 80 \text{ to } 120 \text{ mV.}$$

The combined effect of potassium and chloride would therefore be to give a potential difference of about 100 mV., which is of the same order as that observed in isolated muscle. It is clear that maintenance of the resting potential ultimately depends on metabolism, but we know very little about the intervening links in this process. Recent work suggests that a fraction of the metabolic energy may be directed towards an active extrusion of sodium (Krogh, 1946; Ussing, 1949). A process of this kind would prevent equalization of ionic concentrations and might also have the temporary effect of raising the membrane potential above that required by equations (1) and (2). There must be many other ways in which metabolism might contribute to the resting potential, but this does not reduce the importance of the potassium and chloride systems, which may be conveniently regarded as a storage battery in parallel with a metabolic source of energy.

In the classical form of the membrane theory it is assumed that excitation leads to a loss of the normal, selectively permeable, character of the membrane. If this is so the membrane potential would fall towards zero during activity and there would be no reversal of membrane potential. In order to account for the reversal it will be assumed that the membrane becomes highly and specifically permeable to sodium. In this case sodium ions would tend to enter the fibre faster than potassium ions could leave it and a reversed potential difference would be established. If the membrane became infinitely permeable to sodium its potential should approach the equilibrium potential for a sodium electrode :

$$E_{Na} = 58 \text{ mV. } \log_{10} \frac{(Na)_i}{(Na)_o} \qquad (3)$$

$$E'_{Na} = -52 \text{ mV.}$$

We should not expect to find such a large reversal of membrane potential unless the degree of selective permeability were very great. It is therefore reassuring to find that the average values in muscle and squid nerve appear to be less than the maximum predicted by equation (3) (Nastuk & Hodgkin, 1950; Hodgkin & Katz, 1949).

3. Tests of the Hypothesis

One advantage of this hypothesis is that it can be tested experimentally in a number of different ways. If the active depolarization of a nerve or muscle fibre is due to entry of sodium, it follows that conduction of impulses should be impossible in sodium-free media.

a. Action of Sodium-free Solutions

The action of sodium-free solutions was studied by Overton (1902) and has been the subject of recent investigations by Lorente de Nó (1944, 1947, 1948, 1949a, b) and others (Kato, 1936; Erlanger & Blair, 1938; Webb & Young, 1940; Katz, 1947; Hodgkin & Katz, 1949; Nastuk & Hodgkin, 1950; Huxley & Stämpfli, 1949). There appears to be general agreement that most excitable tissues become reversibly inexcitable when immersed in solutions which do not contain sodium, lithium or certain quaternary ammonium ions. Single nerve fibres from amphibia and crustacea become inexcitable within a few seconds of application of an isotonic sodium-free solution; excitability can be restored by solutions containing sodium in a similar space of time (Hodgkin & Katz, 1949; Kato, 1936). In other preparations, such as frog muscle or the giant axon of the squid, the time required for excitability to disappear may be somewhat longer, but is still of the same order as that predicted on a diffusion basis (Hodgkin & Katz, 1949; Nastuk & Hodgkin, 1950). A frog's sciatic nerve retains its excitability for many hours in a sodium-free solution and there is some difference of opinion about the reason for this. One possibility is that appreciable quantities of salt may be retained in the interstitial spaces as a result of slow diffusion through the epineurium (see Rashbass & Rushton, 1949a,b), but this view is not universally accepted (see Lorente de Nó, 1947). In general, it may be said that the experiments with isolated nerve fibres support the sodium hypothesis while those with multifibre preparations are still the subject of controversy.

b. Effects of Changes in the External Concentration of Sodium

Another consequence of the hypothesis is that the relative magnitudes of the action potential and resting potential should depend upon the concentration of sodium in the external fluid. Thus the active membrane should be unable to give a reversed potential difference if the concentration of sodium in the external fluid were made equal to the internal concentration. The effect of alterations in sodium concentration has now been studied in the giant axon of the squid (Hodgkin & Katz, 1949) and in frog's muscle (Nastuk & Hodgkin, 1949, 1950). In both cases it was found that the magnitude of the reversed potential difference varied with the sodium concentration, in the general manner demanded by the hypothesis. It was also shown that the difference between the action potential and resting potential was increased by solutions containing an excess of sodium. Another interesting point is that the rate of rise of the action potential could be varied over a wide range by changing the external concentration of sodium. This result is clearly consistent with the idea that the active depolarization of a nerve fibre is due to entry of sodium.

c. Ionic Exchange during Activity

A more direct test of the hypothesis has recently been made by Keynes (1949), who has studied the penetration of Na^{24} into *Sepia* axons. He found that stimulation at 100/sec. caused a fifteenfold increase in the rate of uptake of Na^{24}. There was also a considerable increase in the outward passage of Na^{24}, so that it was difficult to decide whether or not activity was associated with a net uptake of sodium. But it seems clear that activity must involve a substantial increase in the permeability to sodium.

The experiments with sodium are closely linked with recent experiments on potassium leakage. Earlier work indicated that activity is associated with a loss of potassium (Cowan, 1934; Fenn & Cobb, 1936; Young, 1938; Arnett & Wilde, 1941) and this finding has now been put on a more quantitative basis. Using an indirect method, Hodgkin & Huxley (1947) estimated that about 1.7×10^{-12} mol. of potassium pass through 1 cm.^{2} of membrane in one impulse in *Carcinus* axons. Using radioactive tracers, Keynes (1948, 1949) reports a potassium loss of 2.1×10^{-12} mol. per cm.^{2} per impulse in *Carcinus* and 4.5×10^{-12} in *Sepia* axons. It is possible that most of the potassium is lost during the falling phase of the action potential and that this loss balances a corresponding entry of sodium during the rising phase. (There is also likely to be some simultaneous exchange of Na and K.) If this view is correct, it follows that the immediate source of energy for the nervous impulse is the exchange of a minute amount of sodium and potassium ions. It is important to remember that the quantities involved are extremely small. Thus the amount of potassium which leaves a 200 μ *Sepia* axon during one impulse is of the order of $\frac{1}{300,000}$ of the total internal potassium. A large nerve fibre should therefore be able to live on its ion store for some time. However, sooner or later the axon must pump out the sodium which leaks in and reabsorb the potassium which it has lost. In this connexion it is interesting to recall that the human erythrocyte appears to be able to extrude sodium (Harris, 1941) and that here there is some evidence to show that sodium extrusion is the active process and potassium absorption is a passive counterpart (Maizels, 1949). If this idea is correct it may simplify the position, since only one secretory system need be considered. But the problem is still a formidable one and no satisfactory hypothesis has yet been put forward.

4. Saltatory Conduction in Medullated Nerve

It would be inappropriate to close this article without referring to recent work on conduction in medullated nerve. There is now a considerable body of evidence to show that conduction in all excitable fibres is brought about by local electric circuits (e.g., Osterhout, 1931; Auger, 1933; Hodgkin, 1937a, b, 1939; Tasaki, 1939b). In muscle and in non-medullated nerve these local circuits spread in a continuous manner and conduction appears to be a perfectly uniform process. On the other hand, medullated nerve fibres show characteristic discontinuities at the nodes of Ranvier, and Lillie (1925) suggested that the high conduction velocity of these fibres might be due to the fact that they conduct in a saltatory manner. On this view the thickly myelinated internodes act as segments of inert cable which allow the impulse to skip from one node to the next with relatively small delay. In recent years much evidence has accumulated in favour of the hypothesis. On the one hand, there are a number of experiments which show that agents block most easily at the nodes of Ranvier (Erlanger & Blair, 1934, 1938; Kato,

1936; Tasaki, Amikura & Mizushima, 1936); on the other, there are experiments which indicate that electric currents stimulate at the nodes of Ranvier (Kubo, Ono & Toyoda, 1934; Kato, 1934, 1936; Tasaki, 1939a; see also von Muralt, 1945). Huxley & Stämpfli (1949) have now subjected the hypothesis to a rigorous test by analyzing the distribution of current in an active fibre. They find that the internodes act as passive, cable-like structures, while the inward current associated with activity is confined to the nodes of Ranvier. This constitutes strong evidence for the saltatory theory; but there remains the difficulty that the myelinated fibres of the central nervous system are commonly supposed to possess no nodes of Ranvier. If this were true, saltatory conduction would be impossible in central fibres and unlikely in the periphery. However, both Cajal (1899) and Bielschowski (1928) described nodes in the central nervous system and their existence has recently been demonstrated by a variety of methods (Hess & Young, 1949; Feindel, Allison & Weddell, 1948; Allison & Feindel, 1949).

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CEREBRAL RESPONSES TO NERVE STIMULATION IN MAN

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1 Cerebral responses to electrical stimulation
  a Responses in a patient with myoclonus
  b Detection of small responses
  c Responses in healthy subjects
2 Afferent nerve fibres concerned in the responses
3 Recording of action potentials in afferent nerve fibres
4 Excitability of afferent nerve fibres concerned
5 Variations in cerebral responses
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The somatic sensory receiving areas in the brains of animals have been mapped by Marshall, Woolsey & Bard (1941) and by Adrian (1941), with particular attention to the results of stimulating cutaneous sensory receptors. Less attention was given to the effects of stimulating proprioceptors, though Adrian mentioned that a prolonged stretching of a muscle caused only a brief discharge in the white matter deep to the sensory cortex. Woolsey, Chang & Bard (1947) stimulated posterior nerve roots electrically, which presumably excited proprioceptive as well as cutaneous sensory afferent fibres, and then found potential changes in the motor cortex precentrally as well as in the postcentral sensory areas. They reported that " the distribution of the precentral responses for various roots supplying the leg suggest that the afferent impulses terminate in a definite way in relation to the pattern of representation in the motor area." Localized modification of the spontaneous activity in the cortex of monkeys was reported by Gay & Gellhorn (1949), who stimulated proprioceptors on the opposite side of the body, and found that the effect was greatest in the particular area of the precentral region related to the part in which muscles were stretched.

1. Cerebral Responses to Electrical Stimulation

a. Responses in a Patient with Myoclonus

Investigations on a patient subject to severe myoclonic seizures (Dawson, 1947b) showed that a large cerebral electrical response could be detected on the scalp after a tap on a tendon or after electrical stimulation of a peripheral nerve. In this patient the responses to stimulation of the arm or leg showed the same distribution in a lateral direction as would be expected in the sensory or motor areas, but in an anteroposterior direction the electrical maximum lay on a line approximately 3 cm. in front of the surface marking of the central sulcus. At post-mortem examination Dr. Greenfield confirmed that this line lay in front of the central sulcus. The question then arose as to whether the response in this subject indicated the normal site of arrival at the cortex of proprioceptive impulses, and was abnormal only in being so large as to be easily detectable, or whether the position in which the activity was greatest was also abnormal. An investigation was therefore begun to see if similar stimuli would produce detectable responses in healthy people.

b. Detection of Small Responses

During the investigations on the patient with myoclonus some difficulty was experienced in measuring the latency of the responses after the stimuli. This difficulty was caused by irregularities in the base-line of the records, due largely to spontaneous brain activity or activity of scalp muscles and to a small extent to random fluctuations in the amplifiers. When a number of records were superimposed with the stimulus artefacts coincident, features occurring at a constant time after the stimulus appeared more clearly, whilst those not regularly related to it produced only a general thickening of the base-line. The start of the response could then be identified more easily and timed more accurately. In the same way it was found that regular deflections in the records, previously too small in relation to the background to be considered significant, could now be detected with certainty. A similar technique was used in radar for detecting signals which were small in relation to random disturbances or interference, and an example of its use is given by Bradfield, Bartlett & Watson (1946). The principle of the method is essentially the same as that used by Francis Galton in 1875 (Galton, 1883), to bring out the features which were common to a number of portraits and to suppress the irregularities which were present only in individual pictures. The value of applying the method to the present work was realized as a result of discussion with Dr J. A. V. Bates, who has also used it for investigations to which reference will be made later.

c. Responses in Healthy Subjects

By the use of the technique described above, it was found that responses to electrical stimulation of peripheral nerve were detectable on the scalps of healthy people (Dawson, 1947a). These responses had the same distribution in a lateral direction as those produced by the same type of stimulation in the patient with myoclonus, but they were only one-fifth to one-tenth as large; they seemed also to be centred, in an anteroposterior direction, nearer to the surface markings of the central sulcus than the responses in the subject with myoclonus. The centre of the disturbance was taken as being deep to the place on the scalp where the potential gradients, plotted with a row of electrodes separated by 3 cm., changed in sign. This is the method described by Adrian & Yamagiwa (1935) and, so long as the potential gradients are symmetrical about the point of reversal, it gives a reliable indication of the position of the centre of the underlying electrical disturbance. In the coronal plane this condition was approximately fulfilled, and it is probable that the location of the area active in the responses, both in the patient with myoclonus and in healthy people, was accurate to within 2 cm. in either direction in this plane. In a sagittal plane the location in healthy people was less satisfactory as, although there was a maximum over the surface marking of the central sulcus, the potential gradients in front of this and behind it were not at all symmetrical. Up to the marking of the sulcus, from a point 6 cm. in front, the gradient was steep.

whilst behind the sulcus it fell only slowly; so the centre of the disturbance was probably not under the marking of the sulcus, although this was where the gradient reversed. An asymmetrical distribution of potential such as this may be accounted for in a number of ways. Of the possible hypothetical arrangements some are not physiologically unreasonable, and these include disturbances either behind or in front of the marking of the central sulcus. Hence it seems that the present methods will not allow accurate location in the sagittal plane of the site of arrival of the afferent volleys in the healthy subject. Although it was not found possible to determine where the activity was centred in the sagittal plane in healthy people, it was clearly differently distributed from that in the subject with myoclonus. It therefore remained important to determine whether or not the nerve fibres which were being stimulated in the two cases, and which were mediating the responses, were the same.

2. Afferent Nerve Fibres Concerned in the Responses

Clinical examination of the patient with myoclonus showed that the adequate stimulus for evoking the jerks was stretching of muscle and that light touch and pin-prick were ineffective in doing so. Electrical stimulation of a mixed nerve in this patient would evoke the cerebral responses, almost unreduced in size, when the shocks were so weak that few motor fibres were being excited. It seemed that the fibres concerned had a lower mean threshold to this form of stimulation than had the motor fibres, and that therefore they probably conducted more rapidly and were of larger diameter than the motor fibres. The group of nerve fibres which conduct most rapidly and have the lowest threshold to electrical stimulation contains fibres carrying impulses from stretched muscle and also, as has been shown by Kugelberg (1944), fibres mediating the sensation of touch. The peculiar power of stretching muscle for producing the responses in the patient with myoclonus, and also the fact that no responses were detected after stimulation of a purely cutaneous nerve, suggested that impulses in proprioceptive fibres from muscle were chiefly concerned. In healthy people on the other hand there was no clinical evidence that proprioceptive stimuli were more potent than any other kind, and the cerebral responses in them to stimulation of a mixed nerve might have been produced by volleys in cutaneous fibres as well as those from muscle. The experiments to be described, designed to test this point, were carried out with Dr J. W. Scott of Toronto. A comparison was made between the effects of stimulating the skin of the thumb and fingers and stimulating the trunk of the median or ulnar nerve through the skin at the wrist. The stimuli were applied to the skin of the hand by placing the thumb in one beaker of saline and the four fingers in another, with the stimulating current passed between the two beakers. It was found that a strength of shock which produced a just perceptible sensation and no sign of muscular twitching in the hand would produce a detectable cerebral response. In this experiment stimulation of some afferent fibres from muscles by spread of the stimulating current might still be occurring. However, the great increase in the shock—enough for it to become very unpleasant in the thumb and fingers—which had to be made before any twitching occurred in the small muscles of the hand suggested that the amount of such spread was probably insignificant with the weaker shocks. Since stimulation of the skin in healthy people produces a cerebral response it seems likely that the response to stimulation of a mixed nerve is also in part due to a volley in cutaneous afferent nerve fibres. In the patient with myoclonus the responses to stimulation of proprioceptors were large and relatively smaller amplifications were used; this may perhaps explain the failure to find responses when cutaneous nerves were stimulated.

In the healthy subject, when the strength of the shock to the thumb and fingers was increased until it was very uncomfortable, and when the small muscles of the hand were twitching slightly as a result of spread of the current, the cerebral response remained smaller in many of its phases than the response which could be produced by stimulating the median, or even the ulnar nerve, at the wrist. This was so when the shock to the nerve was only just maximal for the motor fibres and was not at all uncomfortable. Figure 2 shows in A the cerebral responses to fifty stimuli applied at one-second intervals to the ulnar nerve at the wrist and just strong enough to be maximal for motor fibres. The records in B show the responses to fifty stimuli applied to the thumb and fingers with the shock as strong as the subject could bear. In C are shown the responses to 50 stimuli, applied to the thumb and fingers, which were only just above the threshold for producing sensation. The initial phases of the responses in records A and B are little different in size, but the later phases in A, where the stimulus was applied to the ulnar nerve, are significantly larger than those in B, where the stimulus was to the skin. A strong shock to the skin of the thumb and fingers would be expected to excite a greater area of cortex than would stimulation of the ulnar nerve at the wrist. If the area of active cortex was greater and it was excited synchronously, the change of potential picked up on the scalp with relatively widely spaced electrodes should also be increased; but any such difference in the area of cortex active was not apparent from records such as those shown in fig. 2, A and B.

3. Recording of Action Potentials in Afferent Nerve Fibres

In interpreting the findings described above, little importance may be attached to the size of the cerebral response unless something is known about the characters of the volley of impulses produced by each type of stimulation. It was found that, when the median or ulnar nerve was stimulated at the wrist, the action potential which resulted could be recorded from surface electrodes on the skin over the nerve above the elbow; similarly the action potential which followed the stimulus to the thumb and fingers could also be recorded. The methods used for making these records have been described elsewhere (Dawson & Scott, 1949) and by using them it was possible to obtain some information about the nerve volleys produced by stimulation at the different sites. (Similar methods, which were described by Eichler (1937), had not come to the authors' attention when this work was done.) When the shock to the nerve at the wrist is strong enough to stimulate motor fibres, the centripetal volley will contain antidromic impulses in these fibres, in addition to impulses in sensory fibres of the same and lower threshold. Therefore, when the action potentials are used to compare the activity in sensory fibres produced by different stimuli, allowance must be made for this antidromic volley whenever the stimulus may also be exciting motor fibres. With a stimulus which was

maximal for motor fibres it was shown (Dawson & Scott, 1949) that 70 per cent of the amplitude of the action potential in the nerve was due to impulses in sensory afferent fibres with a lower threshold than that of motor fibres. The remaining 30 per cent was due partly to antidromic impulses in motor fibres and partly to impulses in sensory fibres with the same threshold as motor fibres. Thus when the effects of stimuli to the hand and at the wrist are to be compared, not more than 30 per cent need be deducted from the amplitude of the volley caused by the stimulus to the nerve at the wrist, if the stimulus is exciting motor fibres. After such an allowance had been made the nerve action potential produced by stimulating the thumb and fingers was found to be half the amplitude of that which occurred after stimulating the nerve at the wrist. The action potential from the stimulus to the hand was also 30 per cent longer in duration and had a flatter top than that due to the nerve stimulus. The difference in the size of these two nerve action potentials may have been due to the fact that the stimulus to the hand was exciting only cutaneous afferent fibres, whilst the stimulus to the nerve was also exciting afferent fibres from muscles. But another possible cause of the difference may have been the temporal dispersion of the impulses in the volley, which is indicated by the greater duration and flatter top of the action potential following the skin stimulus. Either or both of these peripheral differences in the results of stimulation of skin or nerve trunk might account for the differences in the appropriate cerebral response.

4. Excitability of Afferent Nerve Fibres Concerned

Experiments have been made to investigate the threshold to electrical stimulation of the nerve fibres chiefly concerned in producing the cerebral responses under consideration. In fig. 1, where one such experiment is illustrated, trace 1 is a time-scale showing 1, 5 and 20 msec. intervals, trace 2 is a record of the cerebral response made from electrodes placed as shown in the diagram, and trace 3 is a record of the action potentials in the left median nerve above the elbow. Trace 4 is a time-scale for trace 3 in 0.1 and 1 msec. intervals and the relative timing and duration of traces 3 and 4 to that of traces 1 and 2 is shown by the notch in trace 1. In A, 50 records have been superimposed without any stimulus being applied to the nerve. In B, an electrical stimulus, strong enough to be maximal for motor fibres, was applied to the median nerve at the wrist once a second, and again 50 records were superimposed. From C to H the shock strength was progressively reduced and it can be seen that the nerve action potential decreases in size more rapidly than the cerebral response. Allowing for the falling out of the action potentials due to antidromic impulses in motor fibres, which would be complete at the shock strength used in record D, these records suggest that the cerebral responses which are being considered are produced mainly by the fibres of lowest threshold in the nerves being stimulated. Of these low-threshold fibres some at least are cutaneous in origin. This is suggested by the fact that with the strength of stimulus used for the records in fig. 1G, and even with the weaker stimulus used in H, which did not produce a detectable cerebral response, the subject reported sensations referred to the peripheral distribution of the median nerve. From the present experiments it is not clear how much of the cerebral response is due to stimulation of these low-threshold cutaneous afferent fibres and how much to stimulation of proprioceptive afferents from muscle. The small size of the cerebral response in record G, when the subject could detect some sensation which was diffusely scattered in the median nerve distribution, suggests that these methods are not likely to be useful for the study in man of the responses to localized tactile or other stimuli.

5. Variations in Cerebral Responses

The use of the technique of superimposing many records of the cerebral response gives a mean form, which would otherwise be difficult to obtain on account of the irregularities in the records. But the method has the disadvantage of masking variations in the size or form of the responses to successive stimuli. A series of records, shown in fig. 3, made during the same experiment as those in fig. 1, but recorded individually instead of being superimposed, shows great apparent variations in the size of the cerebral response. The stimulus, which was of the same strength as that used for the records shown in fig. 1B, was applied to the median nerve at one-second intervals. From the records shown in fig. 1 it was known that when the nerve action potential was reduced by 20 per cent below maximal the mean amplitude of the cerebral responses changed by less than the differences between the individual responses in fig. 3. Since the nerve action potentials in fig. 3 were maximal and varied by less than 10 per cent it seems likely that the variations in size of the cerebral responses recorded in that figure were therefore not caused by any variations in the size of the afferent volleys. Much of the apparent variation of the cerebral responses in fig. 3 was probably due to inadequate relaxation of the subject in this experiment, which produced some irregularity of the base-line. This seems less likely to have been the cause of the variations between the responses in the series of records shown in fig. 4, since the subject was more relaxed in this experiment. In these records the shocks used were applied at one-second intervals and it appears that either the first or the later waves may vary in size or be completely absent. Variations of this kind in the responses to sensory stimuli have been shown to occur in animals (Marshall *et al.* 1941) as a result of cortical activity evoked by a preceding stimulus; but no regular relation between the spontaneous brain activity and the size of the responses to the stimuli was observed. On the other hand, Adrian & Moruzzi (1939) have shown in animals that the activity of the cortical cells discharging into the pyramidal tract is modulated in time with the spontaneous cerebral rhythms in the motor area during dial anaesthesia. In the subject from whom the record in fig. 4 was made, a pair of electrodes 3 cm. apart on the scalp over the sensorimotor area picked up—when the eyes were closed—a considerable amount of activity at 11 cyc./sec., which was apparently spread of occipital alpha rhythm. Whether this spread was a purely passive one, or an active neuronal spread more likely to modulate the activity of the cells concerned in the cerebral responses to stimulation, was not clear, but it seemed worth while to study the effects of applying the electrical stimuli at fixed times in relation to the phases of the alpha rhythm. When this was done the records failed to show any consistent differences between the responses to stimuli at different parts of the alpha cycle, and

CEREBRAL RESPONSES TO PERIPHERAL NERVE STIMULATION

(FIGS. 1—3)

G. D. Dawson

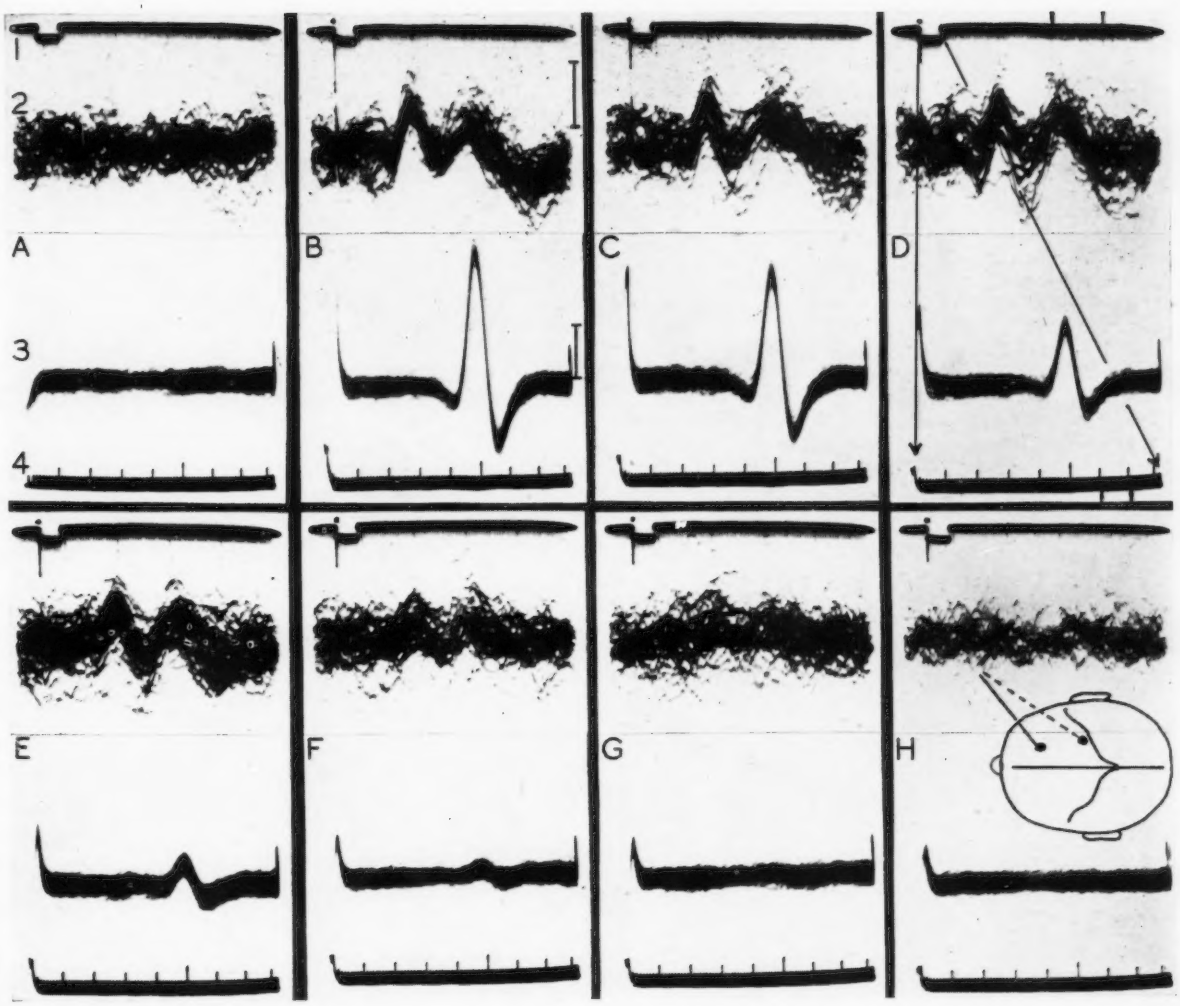

FIG. 1. The 8 records, each of 50 sweeps superimposed, illustrate the relation between the sizes of the action potentials in the median nerve after electrical stimulation at the wrist (trace 3) and the resulting cerebral responses (trace 2). The nerve action potentials were recorded from electrodes on the skin over the nerve above the elbow and the cerebral responses from a pair of electrodes on the scalp 6 cm. apart in the position indicated in H, with the back electrode 8 cm. from the mid-line. The amplifiers were connected in such a way that when the back electrode (dotted line) became positive with respect to the front one (continuous line) an upward deflection was recorded. The stimuli were applied at 1-sec. intervals. The dots above the time-scales indicate the time of stimulation. The short vertical lines in D over trace 1 show 20 msec. for trace 2 ; those below trace 4 indicate 1 msec. for trace 3. The relative duration and timing of traces 3 and 4 to traces 1 and 2 is shown by the notch in trace 1. The vertical lines after traces 2 and 3 in B show the deflection caused by 10 μV. in 2 and 20 μV. in 3

In A, no stimulus was applied to the nerve
In B, a stimulus was applied which was maximal for motor fibres
From C to H, the stimulus strength was progressively reduced, being below threshold for motor fibres in D and just above threshold for sensation in H

The records suggest that the greater part of the cerebral response is produced by afferent impulses in fibres with a lower threshold to electrical stimulation than that of motor fibres

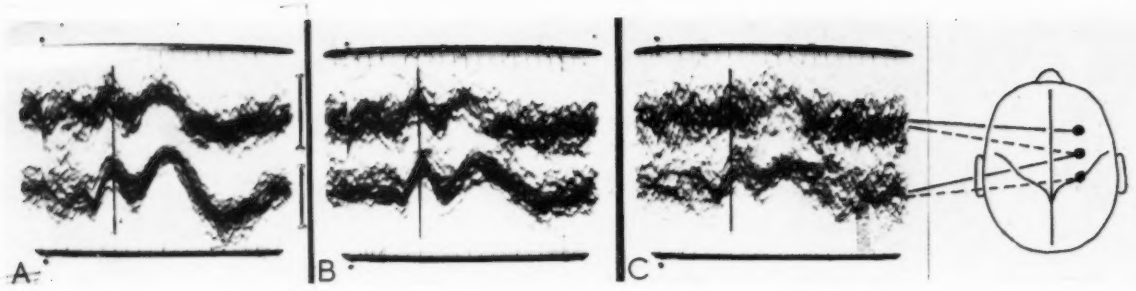

FIG. 2. The 3 records, each of 50 sweeps superimposed, show the cerebral responses to stimulation as follows :

In A, stimulation of the left ulnar nerve at the wrist with a shock just maximal for motor fibres
In B, stimulation of the thumb and fingers with the strongest shock the subject could bear
In C, stimulation of the thumb and fingers with a shock the subject could just detect

The stimuli were applied at 1-sec. intervals. The time-scales show intervals of 1, 5 and 20 msec. and the vertical lines between them show a time-interval of 30 msec. after the stimulus. The dots above and below the time-scales indicate the time of stimulation. The deflection produced by a potential difference of 10 μV. at the amplifier input is shown by the vertical lines at the ends of the traces in A. The scalp electrodes were on a line 7 cm. lateral to the mid-line on the right side and were separated from each other by 4 cm., with the back electrode over the surface marking of the central sulcus. The amplifier was connected as described in fig. 1

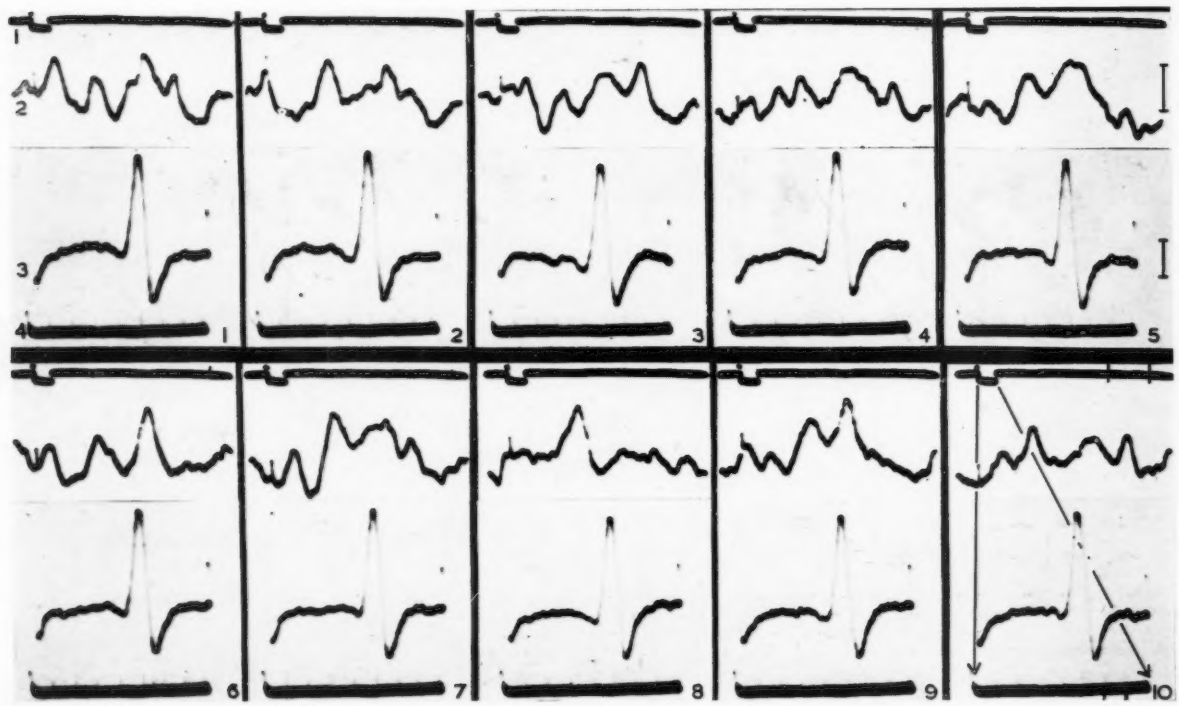

FIG. 3. The 10 records shown were made during the same experiment and under the same conditions as those in fig. 1B, except that they were recorded individually instead of being superimposed. The records show large apparent variations in the cerebral responses in trace 2, without significant alterations in the size of the nerve action potentials in trace 3. The notch in trace 1 indicates the relative timing and duration of traces 3 and 4 to that of traces 1 and 2, as shown in record 10. The short vertical lines above trace 1 and below trace 4 in record 10 show 20 msec. and 1 msec. respectively. The vertical lines at the ends of traces 2 and 3 in record 5 show 10 μV. and 20 μV. respectively

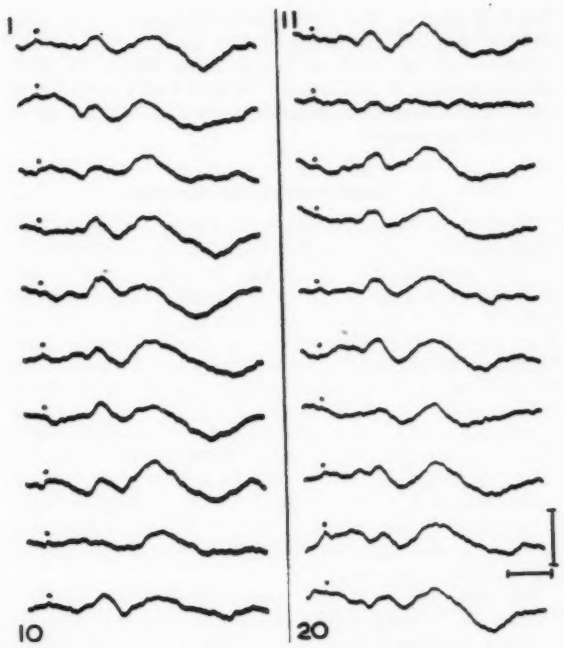

FIG. 4. The records are of 20 consecutive cerebral responses to stimulation of the ulnar nerve. The records were made from a pair of electrodes on the scalp, one over the surface marking of the central sulcus and 7 cm. from the mid-line and the second 4 cm. anterior to it. The cerebral responses are less irregular than those in fig. 3, but they show that either the first or later phases of the response may vary in size or be absent. The vertical line after trace 19 shows 20 μV. and the horizontal line below it 20 msec.

the variations between the responses to successive stimuli seemed to be as great as when they were applied at random, or with the eyes open and little or no alpha rhythm present. There was thus no evidence that the cells responding to the afferent volley were occupied at all by cortical activity at the frequency of the alpha rhythm. This finding is of interest in view of the work of Bates (communication to Second International Congress of Electroencephalography, 1949, unpublished) and of Boreham, Kibbler & Richter (1949), who have shown independently, in the first case by a modification of the superimposition technique and in the second case by a statistical examination of measurements from many single records, that the time of initiation of voluntary movements in man tends to be related to the phase of the alpha rhythm. One explanation of this finding is that a similar relation may exist, in man, between the motor cells and the alpha rhythm mechanism, as Adrian & Moruzzi (1939) showed to exist between the pyramidal discharges and the spontaneous cortical activity in animals. In another sensory field the variations which may occur in both normal and abnormal subjects in the response to visual stimulation with flashes of light, when the rate or phase of the stimulus was altered in relation to the spontaneous rhythms, have been described by Walter & Walter (1949). More recently Cobb (communication to Second International Congress of Electroencephalography, 1949, unpublished) has described in detail regular alterations which have been found to occur in the occipital responses to flash stimuli in conditions of concentration and relaxation of attention. So far no factors which would produce similar repeatable variations in the responses to tactile or proprioceptive stimuli have been found.

6. Conclusions

The experiments described suggest that the cerebral responses which may be detected in healthy man, after electrical stimulation of nerve, are probably produced by excitation of at least two kinds of nerve fibre. One type of fibre is that which carries afferent impulses from cutaneous receptors and the other is probably that carrying impulses from proprioceptors in muscle. The records made through skin show that 70 per cent of the nerve action potential which can be detected is due to activity in fibres with a lower threshold than motor fibres; it is the volley in these low-threshold afferent fibres which produces the greater part of the cerebral response. The relative contributions of the cutaneous afferent fibres and of the afferent fibres from muscle to this group of low-threshold fibres is not clear from these experiments. The records of nerve action potentials also indicate that variation in the size of the afferent volley was not the cause of the variations in size of the cerebral responses to successive stimuli of the same kind; no cause for this variation has yet been found but it seems that, even with submaximal stimuli, it is not peripheral. On the other hand the same methods show that, with different types of stimuli, the peripheral differences in the resulting afferent volleys may alone be enough to account for the considerable differences in the cerebral responses produced.

ACKNOWLEDGEMENTS

The author would like to express his gratitude to Dr E. A. Carmichael for his advice and encouragement, also to Dr J. W. Scott for his help in many of the experiments and in discussion.

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SENSORY DISCRIMINATION

With Some Recent Evidence from the Olfactory Organ

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1 Identification of the stimulus
2 Visual and auditory stimuli
3 Olfactory discrimination
  a Recording of impulse discharges in the olfactory tract
  b Differential analysis of olfactory stimuli
4 Conclusion
References

The vertebrate nervous system receives its information about the outside world by means of signals transmitted by a large number of sensory nerve fibres. The number must be large, because the range of information which one fibre can transmit is small. The fibre signals the excitation of a sensory ending by transmitting a stream of impulses; the frequency of the impulses shows the intensity of excitation at each moment, but there is nothing else to indicate what sort of change has stimulated the receptor. This limitation comes from the nature of the conduction process in the fibre, for a single nerve fibre is a far less able transmitter of information than a single metallic wire, in which a fluctuating electric current can transmit all the inflections of speech or the pattern of a written message. The nerve fibre can send only brief pulses of activity which depend for their transmission on local stores of energy. They must be all alike and cannot bear the stamp of the event which set them in motion.

Ultimately the afferent messages transmitted in this way will modify the stream of efferent messages which are sent out from the nervous system to the muscles. These, too, are made up of impulses, all of the same form and distinguishable only when the fibres carrying them are of different size. Both on the sensory and motor sides, therefore, a large number of nerve fibres must be available if the efferent pattern is to be effectively harmonized with the afferent, i.e., if the animal is to react appropriately to its surroundings.

During the past 25 years the use of electronic amplifiers has made it possible to record the impulses in single nerve fibres, and we have gained new information about the activities of individual nerve cells and sensory end-organs. This led at first to a focusing of attention on the units rather than on the group, for the technique was more suitable for investigating the performance of the sensory nerve fibre than that of the receptor surface or the motor nucleus. Thus problems involving joint action by many units have had less consideration than they deserve. But more recently the study of the large-distance receptors and of the sensory areas of the brain has begun to shift the emphasis back from the unit to the group and the purpose of this article is to deal with a general principle which it now seems possible to trace in the organization of the sensory system.

1. Identification of the Stimulus

Thinking of the individual nerve fibres, one might have supposed that a sensory surface could be regarded as a patchwork of areas, each of which was supplied by one sensory fibre and by that fibre only. The simplified diagrams in the textbooks of, for example, touch spots did nothing to contradict this impression, but it was soon obvious that it was false. Records of the electrical activity in the frog's cutaneous nerve fibres showed that each supplied an area of several square millimetres and that other fibres had endings in the same area, so that the most strictly localized touch could not avoid exciting endings belonging to a number of different fibres (Adrian, Cattell & Hoagland, 1931). The dispersion is often much greater than this in the mammal, as Weddell's histological studies have shown (Weddell, 1941). One nerve fibre to a rabbit's ear may innervate 300 hairs and each hair may be innervated by many fibres.

The wide dispersion and intermingling of the terminal branches of the sensory fibres means that a touch on the skin will send messages to the spinal cord by many paths. Where these terminate there will be a focus of activity corresponding to the point that is touched and a zone of declining activity round it. Thus the pattern of excitation of the skin will be reproduced more or less faithfully and if one or other of the sensory fibres were put out of action it would not seriously affect the reproduction of the pattern. The information will be supplied both by the spatial and by the temporal pattern of excitation, i.e., by the rate of rise and fall of the impulse frequencies in different fibres. And for recognizing the nature of the object which has touched the skin the temporal element may be the more important. Even if the sensory surface did no more than signal the stimulation of different regions the order in which the stimulation occurred would be significant, and in fact the important sensory surfaces never behave as a static receiving screen. In the intact animal a touch which differs from the expected range of contacts will immediately arouse exploratory movements by which the object can be "felt", as, for instance, when something put in the hand is moved about so that the pattern which is available to the brain is compounded of signals from the tactile receptors and from those which show the movement and position of the fingers. Such qualities as roughness and smoothness, softness and hardness, could be judged only by a combination of spatial and temporal analysis.

Contacts with the body surface are signalled to the sensory receiving area of the brain and we must suppose that the identification of the stimulus is dependent on certain events, some of which must take place in that area. But by the time the pattern arrives there the streams of impulses from the periphery will have lost their identity. They will have travelled the whole length of the sensory fibres, the excitation will have been passed on to other neurones, and wherever the transfer occurs some alteration may have taken place, possibly a sharpening of contrasts and usually a reduction in the number of units involved. Thus the effect of an individual sensory

ending on the final picture becomes even less than on the primary signal: it will not be much greater than that of a single voter in a parliamentary election.

2. Visual and Auditory Stimuli

It has been known for many years that an even greater condensation of signals must take place in the eye, for the number of receptors in the retina far exceeds the number of fibres in the optic nerve. But it was not until the impulses in the optic nerve were recorded that it became clear how much interaction could take place between the different pathways. Thus Adrian & Matthews (1928) found evidence of nervous interaction between two points 1 mm. apart on the eel's retina, and Hartline (1935, 1938), Granit (1930) and Granit & Therman (1937) have shown that in frogs and mammals it involves inhibition as well as facilitation. Again, therefore, the contribution of the individual receptor is likely to be submerged in the composite pattern.

With vision, as probably with touch, there are certain parts of the receptor surface where there is less intermingling of pathways. At the macula lutea some of the cones seem to have private pathways through the retina to single fibres in the optic nerve. This may be necessary to give the extreme detail with which the central visual pattern must be reproduced, but the insulation of the pathways from one another is an inference from retinal histology and may turn out to be incomplete.

Both with touch and vision we interpret the stimulus in spatial and temporal terms, and it is therefore not surprising to find the spatial and temporal patterns reproduced in the brain. With hearing, however, there is no spatial quality about the stimulus, yet there is already abundant evidence to show that auditory stimuli are distinguished, like tactile and visual stimuli, by differences in the spatial and temporal excitation pattern. The evidence is partly old and partly new. Helmholtz's resonance theory supposed that the cochlea was so arranged that each part of the basilar membrane would tend to resonate to a particular note. The various objections raised to the theory have now been set aside by the work of Galambos & Davis (1943) on the impulses in the auditory nerve fibres. They find that a pure tone of small intensity excites only a limited region of the basilar membrane—near the basal turn of the cochlea for high tones and near the apex for low. As the intensity of the sound is increased the extent of the excited area enlarges, but the region of maximum excitation remains where it was. Thus the distribution of excitation along the basilar membrane from moment to moment will give all the information needed to specify the sound.

As with tactile and visual signals, the pattern is passed on to the brain, condensed and possibly sharpened, but preserving its spatial arrangement. Tunturi (1944) has found that in the dog the different segments of the basilar membrane are connected with different points in the auditory area, just as the different parts of the body surface are connected with different points in the somatic sensory area. With a high note the cortical activity will be at the front, and with a low note at the rear, and as the sounds change in pitch the region of maximal activity will shift in the basilar membrane and in the auditory area of the brain. There the information is conveyed as before by the temporal as well as by the spatial pattern. A voice will give several peaks of activity, shifting to and fro along the cortical strip in a characteristic fashion, and our recognition of the voice will depend on the particular sequences which occur.

These results bring hearing into line with vision. In both the eye and the ear the general plan seems to be that a large area closely packed with receptor endings is set in the organ, the structure of which ensures the analysis of the stimulus in spatial terms. The camera arrangement of the eye projects the visual scene on the retina: the resonating system of the cochlea projects different sound frequencies on to different parts of the basilar membrane. It is to be noted also that, in both, the information is transmitted to the brain in the same form, i.e., with the intensity indicated by the impulse frequency and the number of fibres in action. The earlier records from the auditory nerve suggested that the impulse frequency was fixed by the pitch of the sound, but we know now that it varies over the usual wide range and indicates loudness and not pitch.

As in the eye, so in the ear the contribution of any one fibre of the auditory nerve will be relatively unimportant, because even with the feeblest stimulus the message will be carried by a group of nerve fibres. With a loud note, more than half the basilar membrane may be excited. Thus the failure of a few of the receptors would make little difference to the general balance of the pattern. A larger failure might be detected by careful audiometry, just as a scotoma in the field of vision can be detected by careful perimetry, but the subject would be unaware that he was deaf to a particular tone or blind in a particular part of the visual field.

There is, however, one important difference between the signalling of visual and auditory stimuli. So far as we can tell, the most complex sound will be analyzed into a spatial and temporal pattern by the mechanism of the inner ear, but in a complex visual scene there will be differences of colour as well as of light intensity. The analysis of colour undoubtedly depends on the properties of the visual receptors rather than on the optical mechanism of the eye, and if the contours of objects are disclosed to us by the pattern of excitation in the striate area, the same pattern cannot also disclose the colour of the object. There are some grounds for thinking that the colour will affect the temporal pattern, but at present this is little more than a guess.

3. Olfactory Discrimination

The eye and the ear are the distance receptors most important to man, but to many animals the nose is the chief guide. In the last few years an attempt has been made in Cambridge to find out how smells are distinguished, and the results, though still very far from complete, point to a fundamental likeness between all three distance receptors (Adrian, 1948). When we consider the olfactory organ, we seem to be confronted with sensory experiences which have no spatial quality and no components like the scale of pure tones which we recognize as building up sounds. But an immense variety of smells can be distinguished and, like the eye and the ear, the olfactory organ has a large sheet of receptor endings and an elaborate structure to contain it.

The receptor sheet is spread out on folded partitions and is exposed to the air in the narrow spaces between them. This air is in free communication with that drawn into the lungs at each breath, for the olfactory organ is set above and behind the main airway through the nose, so that the pressure

gradients will cause some movement of air in the olfactory spaces. The area covered by olfactory receptors is comparable in size to the retina, but the nervous layers of the retina are represented in the olfactory system by the olfactory bulb, which receives the nerve fibres from the receptors. Here synaptic transmission takes place and the signals, greatly condensed, are passed on by the fibres of the olfactory tract in the same way as the signals from the retinal receptors are conveyed by the fibres of the optic nerve.

a. Recording of Impulse Discharges in the Olfactory Tract

To make clear records of the electrical activity in these fibres the animal must be under anaesthesia deep enough to suppress the spontaneous discharge from cells in the olfactory bulb. It is then found that impulse discharges occur in the tract fibres whenever air containing an odorous substance is drawn through the nose, and we can look for some characteristic difference in the discharges set up by different smells. What has been found is not that there are receptors with specific sensitivity uniformly distributed over the olfactory epithelium—such receptors may exist, though the impulse discharge technique is scarcely precise enough to reveal them—but what is revealed is that with different smells there may be large-scale differences in the level and evolution of the excitation in different parts of the receptor surface. This can be shown by making simultaneous records from different parts of the olfactory bulb. In the rabbit (the most convenient animal to use) an insulated wire electrode thrust deeply into the oral part of the olfactory bulb will record from the fibres which are in touch with receptors in the oral and more accessible part of the olfactory epithelium, and an electrode leading from the aboral part of the bulb will record from fibres in touch with the receptor surface at the back, furthest from the main air current through the nose. It is found that there are two classes of odorous substance which can be clearly distinguished by their relative effect in these two regions. Esters and compounds containing oxygen as well as carbon and hydrogen produce a greater excitation in the front areas, and hydrocarbons and oils generally produce a greater excitation at the back. Either class will stimulate in both regions if the smell is present in high enough concentration; but there is still a characteristic difference in the evolution of the discharge. With the esters it starts abruptly and is very soon over: with the oils it starts more slowly and usually outlasts the period of inspiration. Thus fruity and oily smells could certainly be distinguished by the distinctive spatial and temporal pattern of excitation in the receptor surface.

b. Differential Analysis of Olfactory Stimuli

On the analogy of the eye and the ear it would seem probable that in the olfactory system the analysis is brought about by the general arrangement of the olfactory organ rather than by a differential sensitivity of the receptors in different parts of it. The general arrangement will certainly lead to considerable differences in the stimulus to the front and back regions. The air current will be more rapid in the more accessible front passages. The air reaching the back will have already passed over much of the epithelium and may have lost some of the odorous molecules on the way. There may be more or less water vapour in the two places and differences in the fluid covering the receptors. Such differences, imposed by the structure of the olfactory organ, might well make stimulation by the esters more effective in front and by the oils more effective further back; but it is equally possible that the receptors in the two regions are not exactly alike in their sensitivity to different smells—there is not yet enough evidence to decide. What is clear, however, is that owing to this regional analysis there may be large-scale differences in the pattern of excitation set up by two kinds of smell.

What is not yet clear is the extent to which olfactory discrimination depends on such differences of pattern. They have been shown to exist for only two classes of odorous substance; it does not at all follow that there is a distinctive pattern for every smell that we can recognize. But certainly if there were other differential effects of the same kind, leading for instance to a different distribution of excitation with small and large molecules, the range of analysis would be much greater. And if, in addition, there are some regions where the receptors in general are more readily excited by a particular class of compound, the possibilities are immensely extended. It must be remembered that both the temporal and the spatial distribution of the excitation is probably significant and that the latency of the discharge may vary both with the velocity of the air current (which will differ from one part of the olfactory organ to another) and with the chemical and physical properties of the stimulating molecules. At all events, the evidence as far as it goes supports the view that large-scale differences of pattern can occur, and there has been no indication that the olfactory epithelium is a uniform mosaic of receptors, each with specific affinities for certain kinds of smell. Indeed, if it were, there would be no obvious reason for the large sensitive surface and the complex arrangement of the olfactory organ.

On this view the range of olfactory discrimination will depend partly on the size and complexity of the organ, which has to produce the characteristic pattern for each smell, and also very much on the ability of the central nervous system to discriminate between two olfactory patterns which are nearly alike. If we had the dog's much larger and more elaborate olfactory organ, it would not necessarily follow that we should distinguish many more smells than we do at present; and if the dog had ours he might still have a range of discrimination wider than we have though not as wide as that of a normal dog.

4. Conclusion

It will be seen, then, that from the study of these three kinds of distance receptor organ the same general principle emerges. This is that the signals from them can be recognized or differentiated because the stimulus is analyzed not so much by a large number of receptors of different properties but by the sense organ itself, so that a characteristic pattern of excitation is formed on the receptor surface. The receptors may well differ in range and sensitivity, and the activity of a particular class will assist the recognition of the pattern, but the general balance of activity over the whole surface and the way in which it changes from moment to moment is determined by the structure of the organ in which the receptors are contained. In the eye they are contained in a camera, in the ear they are fixed to a system of tuned resonators, while the olfactory organ seems to act as an analyzer for molecules of different physical and chemical properties. Since recognition

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LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX

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1 Structure of the cortex
2 Motor cortex
3 Physiological neuronography and suppressor areas
4 Cortex and autonomic functions
5 Parietal-temporal fields
6 Levels of consciousness
References

A man who has the curiosity to look back at the physiological textbooks of about a hundred years ago cannot withhold admiration for the insight shown by the comparative anatomists of that time in deducing the probable uses of the different parts of the central nervous system. They had already firmly chosen the optic thalamus as the chief relay station for sensation, and if they erred in believing that the caudate nucleus and striatum were the chief motor ganglia they were wrong only in calling them "chief". The belated discovery of excitability of the cortex in 1870 (belated because it lagged more than 70 years behind Galvani's discovery of the excitability of peripheral nerve) found the scientific world in a mood of ready acceptance, so well had Hughlings Jackson prepared the way by clinical inference. Once the resistant crust had been broken progress was rapid, especially in the hands of Ferrier, Schäfer and Horsley. Topographical maps of the motor area must indeed have been exciting things to look at for generations who had been taught that the function of the cerebral mantle was to fabricate "the Will", the commands of which were carried out by lower "nervous hands" and principally by the spinal cord. Almost concurrent with the newer exploration of the cortex were the histological researches of Cajal. It was his ability to demonstrate the nerve cell in continuity with its axon and dendrites as a discrete unit that opened the way for intelligent experiment. Before Cajal's time the cortex had appeared to be a meaningless tangle of cells and fibres. So great was the illumination shed by the new histology that Cajal (as Sir Charles Sherrington has said) was the real begetter of the neurone theory commonly ascribed to Waldeyer (1891). The importance of the neurone conception went far beyond that usually attributed to it, namely that it was a biological unit in which the survival of the axon depended on the cell and vice versa. The importance that others saw in it was that the nervous impulse passed in one direction only, i.e., dromically, so that revelatory experiment became possible by tracing the expected passage of impulses. Brilliant use of this property was made by Sherrington, who painstakingly built up a coherent story of integration in the spinal cord. The relatively simple structure of the cord made this project successful. Sherrington substantiated the claim that Marshall Hall had passionately held (but could not prove) 50 years before—that the spinal cord was an organ and not a large bundle of conducting fibres. By contrast, what we lack still and probably for very long will continue to lack is an equally clear insight into the integration of the brain as a whole.

1. Structure of the Cortex

The structure of the cortex naturally attracted many observers. It quickly became apparent that the cortex was not made in a homogeneous and identical pattern but that there were differences almost as one passed from one gyrus to the next. It was thought that these differences must be highly significant and before long several maps of cortical structure, now famous, made their appearance. The best-known maps were those of A. W. Campbell (1905), Grafton Elliot Smith (1907), K. Brodmann (1909), C. & O. Vogt (1919) and von Economo & Koskinas (1925) (for Brodmann's map, see fig. 1). The areal differences depended on cell size, cell shape and density of cell population, and on the position and thickness of interspersed fibre layers. Authority had been given to the view that the chequer-board cortex did in fact represent a pattern of significant functional differences by two discoveries. The unique pattern of the calcarine striate area was found to correspond accurately with the visual area; later O'Leary & Bishop (1938) demonstrated, by stimulating the rabbit's optic nerve and picking up potential-fluctuations in the occipital region, that the electroencephalographic relationships tally very closely with the extent of the anatomical striate area. A further point was that the motor area was found by the Russian biologist Betz (1874) to contain a number of strikingly large pyramidal cells, which caused the part immediately abutting on the fissure of Rolando inhabited by them to be later called "area giganto-pyramidalis". Much more recently it has been shown that the pyramidal tract, tentatively named "Pyramidenstrang" by Türck (1851) when he first ingeniously studied the descending degenerations in the spinal cord, originated from many cells besides the Betz cells (which are, in fact, calculated to contribute not more than 2–3% of the pyramidal fibres) and further that these cells were not, in anthropoids and men at least, the only

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depends on the general excitation pattern, the interaction and concentration of pathways will not prevent the recognition of the stimulus and, as happens with vision, the interaction may assist it by sharpening contrasts and emphasizing details.

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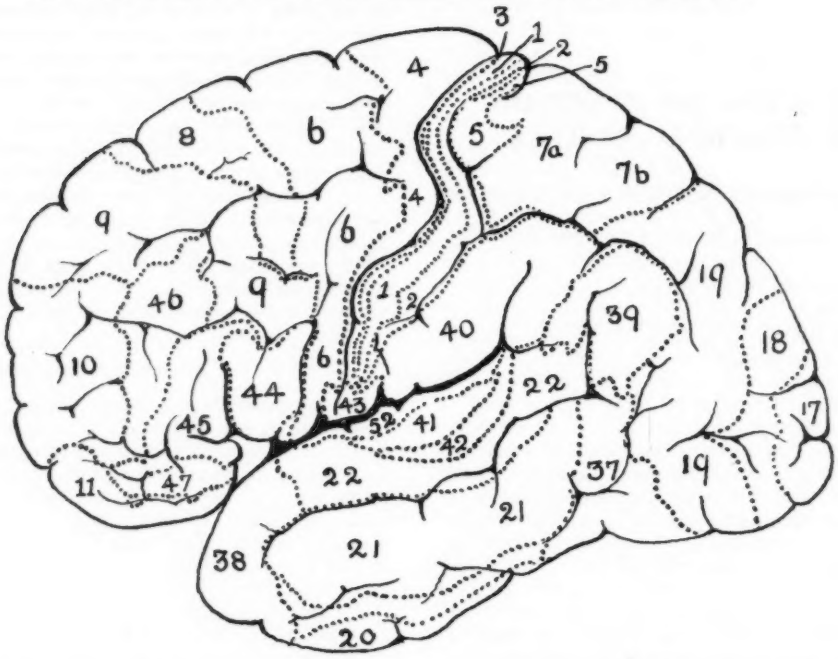
FIG. 1. BRODMANN'S CORTICAL AREAS, DELIMITED BY HISTOLOGY



ones from which movement could be excited by cortical stimulation. It is not as generally appreciated as it should be that the pyramidal tract was so called not because its fibres originated in pyramidal cells but because it ran through the pyramid of the medulla oblongata. The pyramid had been thought to be the pathway of motor power for generations before its exact location in the cord was discovered by Türck, and even he did not know for certain whence it came. Ignorance of this piece of physiological history can even now lead to confusion.

It gradually became clear that the histologist had provided both physiologist and clinician with more facts about the cortex than they could use. The mind could easily grasp the plan of motor nuclei in brain-stem and spinal cord, whilst the spinal dermatomes and the afferent pathways presented no insuperable obstacles to exploration. But what could be the meaning of the six-layered cortex—this stratification of cell and fibre layers? It had to be admitted that although a single-layered cortex would have been more easy to understand, such a one could surely not have provided an adequate machinery for the limitless variety of human behaviour. Research today is no little concerned with an attack on the meaning of cortical structure, in the hope that it may have a simpler explanation than at present appears. It is possible that parallels may eventually be found in electronic "mock-ups", for certainly scrutiny with the microscope has so far failed to indicate a meaning. Possibly the new quantitative survey of cell population in different areas being undertaken by J. Z. Young at University College, London, may be suggestive. But it may be that the structural differences between various cortical areas are not so great or so important as was once forecast (see Lashley & Clark, 1946). By using microelectrodes it has been shown that the production of the potential-pattern of the electroencephalograph seems to be a function of the whole thickness of the cortex and not of any one single layer. It differs, so far as we yet know, not so much in kind as in intensity in different regions.

Perhaps we have been too "cortically minded", have thought too much of, and have searched too readily among, cortical structures during the last decades, to the detriment of our understanding of subcortical and brain-stem mechanisms. Have we not assumed too readily that these last were capable of only the crudest synthesis, and were we not wrong in thinking so? It seems to me that much of the immediate future of neurophysiology will centre on the correlations between the higher and lower levels of Jacksonian integration, and that the lower levels have already won greater respect than they used to have. Changing views about the supreme importance of the cortex might be illustrated by the motor area.

Some of the difficulties that beset the clinician in correlating his bedside observations with the laboratory findings of the neurophysiologist arise from the fact that the latter is much more concerned with, and much more interested in, the cortex of apes, monkeys and the lower animals than he is in man's. The physiologist appears to be more impressed by a chart such as the famous diagram of Grünbaum & Sherrington (1901) of the orang-utang's stimulable cortex than he is by Penfield's topographical charts from 200 human beings (see Penfield & Erickson, 1941). Perhaps I exaggerate if I say that since Penfield's charts are not identical with Grünbaum & Sherrington's in the matter of a separate discrete secondary pre-motor area for eye-turning, then so much the worse for Penfield! But the enquirer must be warned of the differences in outlook between the pure physiologist and the neurologist. Each studies the creatures which most readily lend themselves

to observation—sub-human on the one hand, human on the other. It is difficult to be unbiased in these matters, but it seems to be strikingly true that the clinician is more ready to learn from all sources than is the physiologist, who would do himself no harm by now and again checking his results against roughly comparable results due to disease in man. Much animal experiment is only roughly transferable to man ; structures gain in importance as the scale is ascended—compare the crippling effect of total excisions of motor areas in the chimpanzee with similar removals in the cat. But the laboratory worker plays the laboratory game according to the conventions of his fellows and is instructed not to show interest in " applied physiology ", which is for some reason a debased activity (see Fulton, 1949a). But we may properly ask whether " pure " physiology exists and whether it is not always " applied."

2. Motor Cortex

The motor cortex represents movements, fragments greater or smaller of a useful action, rather than muscles (as Walshe, upholding the doctrines of Jackson and Sherrington, has repeatedly said in his scholarly reviews of motor function). Some have thought that refinements in liminal stimulating currents elicited single muscle twitches ; and there is no real reason why this should not be so. The suggestion would perhaps seem less shocking if the muscles had never been named and the experimenter saw a twitch in a portion of a complicated muscle mass. Certainly both animal and human behaviour is a matter of co-ordinated movement of large muscle masses, innervated presumably by hundreds or thousands of motor cells.

We are as far off as we were 300 years ago from knowing how the brain uses the motor cortex. The beautiful researches of Sherrington with Graham Brown, and with Leyton[1], had established finally not only the topographical lay-out of the motor cortex but also its essentially pre-central situation (see Leyton & Sherrington, 1917 ; Grünbaum & Sherrington, 1901 ; Brown & Sherrington, 1912). But these researches showed that the motor cortex was not like a pianoforte where pressure on one key invariably produces the same note. It was a somewhat refractory piece of living nervous tissue which *on the whole* gave such and such a result at any given point but which was subject to slight variation—variations that became more apparent the longer the experiment lasted. The anterior edge of the excitable motor cortex seemed to wax and wane, becoming gradually more extended as " facilitation " developed. Every neurosurgeon knows how true this is of the human motor area. Sherrington had shown also that the responses might be reversed, that from a given stimulated spot extension might be replaced by flexion. By varying the parameters of stimulation, more recent explorations have carried knowledge of " reversal " and " deviation " of response much further. Fulton (1949b) has shown that a change of wave shape and intensity of the cortical stimulus alters the motor response in a limb even though the electrode is not moved. Innovations in the kinds of electrical stimuli applied to the cortex are opening up new fields because not only are the motor results different from those obtained by classical faradic methods but silent areas are not so unresponsive as they were to older techniques. This matter has been carried further by Liddell & Phillips (Festschrift für C. & O. Vogt, in the press) who have obtained by square waves of excitation single ' flick ' responses in the limbs that vary interestingly in their incidence with the intensity of the stimulus almost regardless of the position of the electrode. The importance of these newer stimulatory methods is that they permit of more intelligible surveys of the motor cortex than were possible in the days when increase in intensity of the faradic current then employed resulted inevitably in a violent epileptic fit that rendered further observation nugatory.

The recently published researches of Denny-Brown & Botterell (1948) bring emendations too, the most important being that partial excisions of Brodmann's area 4 depress all motor behaviour in the contralateral limbs and that incomplete excisions, although affecting one body segment more severely than another, do in fact depress all the opposite side. This view is supported by Lashley's observations. Lashley holds that the motor areas are " more concerned with the maintenance of excitability and the regulation of postural reflexes than with the excitation and control of finely integrated movements " (Lashley, 1924). Certainly excitation in man never, in my own experience or in the wider experience of Wilder Penfield, has caused anything more than a fragment of a recognizably useful movement, something that could be imagined as a bit of a skilled movement. But more often the abrupt twitches are no more than caricatures of anything that a man normally does with his limbs. Denny-Brown & Botterell (1948) found that stimulation of the motor cortex abutting on the central sulcus evoked more localized effects in distal joints than were obtained from stimulation of the anterior parts of that area, which seemed to be more concerned with postural movements of the proximal joints. The highest digital skills were most posterior. But the whole function of area 4 was less specific than has been so far taught. Spasticity developed after all excisions of the motor area. This vindicates the claims put forward by Walshe in several papers (Walshe, 1944, 1947), for he was unable to reconcile clinical observation with certain experimental findings of Fulton. The permanent flaccidity reported by Fulton & Kennard (1934) after excision of area 4, and spasticity after excision of area 6, was not confirmed by Denny-Brown & Botterell (1948). The flaccidity said by Tower (1944) to result from section of the pyramids remains for the moment a mystery. Flaccidity does actually occur for a time after complete motor excisions but Denny-Brown & Botterell (1948) attribute it to " pyramidal shock ", which does not persist indefinitely. It is prevented or shortened in duration if parcels of Betz cells are left behind during the excisions. Spasticity is held to be a disorder of the intimately associated neurones connecting the motor area to the mesencephalic and bulbar (tectal) mechanisms. It is this disturbance which induces the most characteristic features of hemiplegic spasticity. Denny-Brown & Botterell (1948) conclude that " . . . area 4 acts as a potentiator and integrator of movement more directly related to the thalamus and the pontospinal mechanism than to the remainder of the cortex." When we read this conclusion we may recall Hughlings Jackson's cautious belief that certain convolutions are only *more* concerned with movement than others—the monopoly was not absolute. And experiments clearly show that far more movements are obtainable from the motor area than elsewhere, but in some circumstances movements have in fact been evoked from most of the

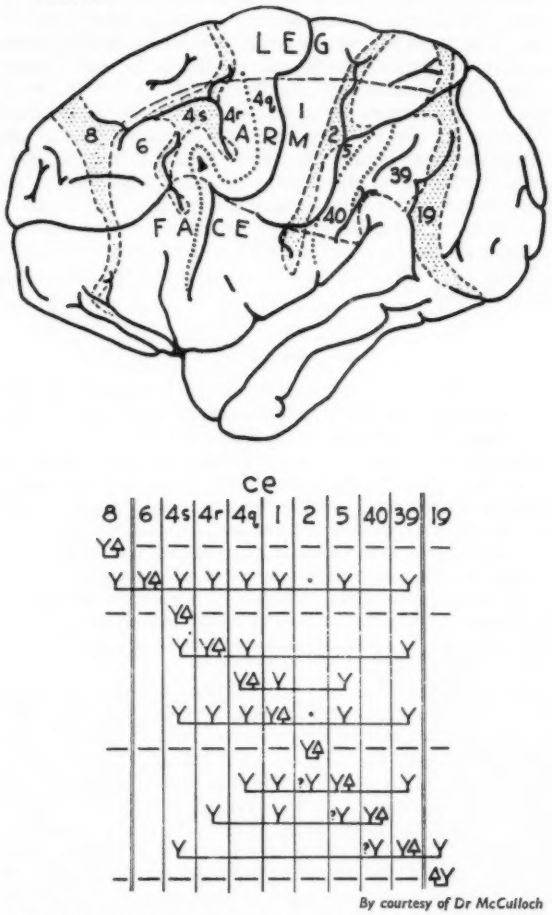
[1] A. S. F. Leyton was earlier known as Grünbaum ; earlier publications therefore appeared under the latter name.—Ed.

convolutions (see the work of Penfield, Dusser de Barenne, and others). Area 4 in man is said by Lassek (1948) to contain about 34,000 Betz cells; these are more numerous at the mesial end of the motor area, i.e., the leg area. The significance of this particular distribution is puzzling. In numerical contrast the pyramidal tract at the level of the medullary pyramid contains roughly 1 million fibres, of which some 40 % are non-medullated, and great numbers are very fine indeed. The number of large fibres such as would furnish a fast-conducting system is roughly the same as the number of cortical Betz cells. The origin and purpose of the slow-conducting fine fibres are not known; some may be autonomic. But it is quite certain that the pyramidal tract must contain great numbers of fibres from sources other than the Betz cells. At the moment all available evidence (e.g., cord degeneration studies after decortication in animals and after hemispherectomy in man) indicates that all the pyramidal fibres spring from the cortex. The histological sections of the cord after cortical excisions (Leyton & Sherrington, 1917) showed fewer degenerated axons than would have been expected and moreover that they were scattered in a random fashion in the tract. There seems to be no authority for Foerster's diagram (1927) of a neatly laminated pyramidal tract, with the short distance axons nearest the central grey matter for convenience of access. It was a pretty picture, but it was a piece of artistic imagination—but then Foerster was a highly imaginative man.

3. Physiological Neuronography and Suppressor Areas

The discovery by Dusser de Barenne that a piece of filter paper 3–4 mm. square soaked in a saturated solution of strychnine sulphate was a powerful and long-lasting stimulator of cell bodies, but not of axons, provided the experimental physiologist with a new laboratory tool (Dusser de Barenne, 1933). In fact the discovery of different kinds of both electrical and of chemical stimulation has caused some formerly " silent " areas to yield information. The results of strychnine stimulations such as these could be used in two ways. It could be a method of direct observation, such as by application to an animal's cortical sensory area in topographical sequence, with watch kept on the body segment in which the stimulatory effects (usually unpleasant) were evidently experienced. Or it could be used in combination with electronic pick-ups to discover the interrelationships of cortical areas. By this means many of the fibre connexions known by anatomical dissection were discovered to be what they seemed—bundles of functional association or perhaps inter-cortical projection fibres. It has proved its importance by verifying the direction in which the nervous impulses passed, a fact on which pure dissection could pronounce no judgement. It has been possible to do a good deal more than that by quickly identifying the relationships between cortex and thalamus and hypothalamus. In the main it verifies the painstaking and beautiful experimental anatomical studies of Le Gros Clark and of Earl Walker (see, for example, Le Gros Clark, 1932a, 1932b; Walker, 1938). This work lies along the lines already mentioned, a retreat from the study of areal differences in the cortex to that of cortical linkages with deeper structures. But the other point just mentioned stands out very clearly: the previously " silent " areas are now stimulable and the effects of stimulation can be picked up by electronic recorders.

FIG. 2. McCULLOCH'S MAP OF SUPPRESSOR STRIPS AND HIS ANALYSIS OF CORTICAL INTER-RELATIONS



By courtesy of Dr McCulloch

Map indicates areas of sensory and adjacent cortex, distinguishable by physiological neuronography, in chimpanzee (*Pan satyrus*). Below are diagrams indicating maximal axonal field disclosed by repeated strychninizations in area marked △. Horizontal dashes indicate suppression of electrical activity; Y indicates area fired; ce refers to central sulcus; double vertical lines indicate anterior and posterior borders of sensory cortex. (Reproduction of fig. 91b, in *The precentral motor cortex*. See McCulloch, 1944.)

Amongst the most interesting and unexpected of these results has been the discovery by Dusser de Barenne & McCulloch (1934) of suppressor areas, work extended by those observers, by Bailey and by Garol. Four suppressor strips are now known, two frontal and two parietal (see fig. 2), making five in all, including Brodmann's area 24 discussed below. Strychninization of these strips leads to the extinction of spontaneous electrical rhythms in the cortex and renders the motor area silent to stimulation; tendon reflexes may be temporarily abolished. The effects may not come about for 20 minutes and may last as long or longer. Garol & Bucy (1944) found that stimulation of strip 4S leads to motor relaxation in the contralateral limbs in man. The part played by

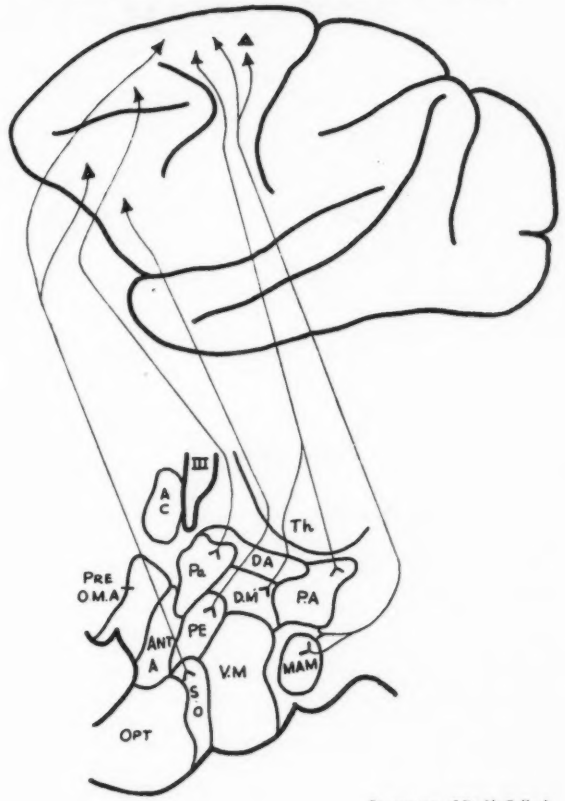
these contributory cortical areas in the normal synthesis of behaviour is neither known nor easily foreseen. Probably nothing exactly like the suppression that can be obtained experimentally actually occurs in health. But it is well enough known that brain activities must be a balance of activation and inhibitions. It is presumed that the suppressor strips must be part of the inhibitory system. Each suppressor area is associated with a major functional subdivision of the cortex (see fig. 2): area 8 with the associative activity of the frontal pole, area 4S with motor control, suppressor area 2 with sensation, and area 19 with vision. McCulloch (1944) has shown that all have connexions with the caudate nucleus and some parts of the corpus striatum, and these structures are supposed to block thalamic impulses from reaching the cortex. Ritchie Russell (1947) has suggested that cortical injuries that coincide with these strips are more likely to produce fits than those in other parts of the cortex.

4. Cortex and Autonomic Functions

Another important suppressor area appears to be Brodmann's area 24 or the cingulate gyrus. Long considered to be part of the rhinencephalon and olfactory system, Le Gros Clark (1948) and von Economo & Koskinas (1925) see in it a highly important vegetative centre. Pupillary dilatation, pilo-erection, vagal slowing of the heart, and respiratory slowing and arrest for as long as 25 sec. have been observed on stimulation of different parts of the cingulate gyrus. It appears also to be a secondary motor area, since tonic bilateral movements of the limbs have also been observed to follow stimulation. Strychninization causes widespread and deep suppression of electrical activity in the rest of the cortex, a suppression mediated, according to McCulloch (1944), by the caudate nucleus. Ablation of the cingulate gyrus leads to considerable change in personality in monkeys—disappearance of shyness and hostility, and a concomitant lack of social sense so that the monkey will walk on its fellows or take food from them without expecting reprisals. How far any of these functions are applicable to man is not known but probably its dominance in all directions is less pronounced than in the macaque. Confirmation, however, is required.

Another important autonomic area lies on the orbital surface of the frontal lobe, lateral to the olfactory tract but close to its lateral root. This is Brodmann's area 13. Stimulation of this area was found long ago by W. G. Spencer (1894) to lead to respiratory arrest. Lately this area has been much studied by Bailey & Sweet (1940), and by Livingston *et al.* (1948). Stimulation of a corresponding area (which is perhaps area 47) has been observed to lead to respiratory arrest and a slow moderate rise in blood-pressure. Strychninization of this area has been shown to cause firing of certain of the hypothalamic nuclei, paraventricular and posterior (Warren McCulloch, Bailey and Ward) (see fig. 3). Another interesting observation has been that prolonged faradization of this area in the cat caused ischaemia of the renal cortex with a shunt of blood-flow similar to that discovered by Trueta *et al.* (1947) at Oxford. Vasodilatation of the extremities generally followed excision of these areas in monkeys but also rendered them restless and over-active (Livingston *et al.* 1948). Autonomic reactions such as pilo-erection were recorded by Fulton and his co-workers from the motor area or its immediate environs. Connexions with the hypothalamus are probably weakly and thinly sown in the cortex; the

FIG. 3. McCULLOCH'S DIAGRAM OF REVERBERATIONS IN HYPOTHALAMIC NUCLEI FROM STIMULATION OF THE ORBITAL FRONTAL CORTEX



By courtesy of Dr McCulloch

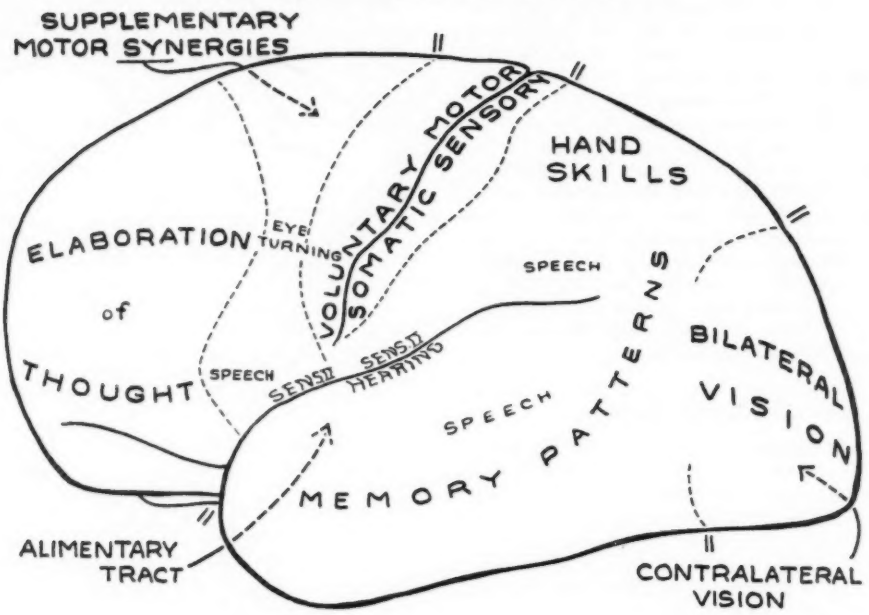
main concentrations so far found have been those mentioned on the orbital surfaces and in the cingulate gyrus. Bucy & Pribram (1943) have recorded a case of localized sweating from a glioma affecting area 44.

5. Parietal-Temporal Fields

It has been said that the anatomist of 40 years ago had high hopes that clinician and neuropathologist between them would be able to substantiate the functional individuality of a great number of histologically different areas. Electrical stimulation of the brain in animals and later in man, although it gave fascinating results, accounted when all was said and done for a surprisingly small portion of the total cortical area. Vast tracts remained which were silent to stimulation. It was in these regions that the clinician might hopefully be expected to discover a coherent description of function from human beings able to give an account of their subjective experiences. This proved to be true of certain regions, notably those concerned with language and sensation.

An example already existed from pre-stimulation days, namely, Broca's use of Dax's discovery that dysphasia required usually a left-sided lesion. Broca selected the posterior end of the third left frontal convolution as the area

FIG. 4. LOCALIZATION OF FUNCTION



By courtesy of Prof. Wilder Penfield

concerned with language. He chose this because Dax had shown that the lesion producing dysphasia must be left-sided; Broca chose the third frontal convolution because this lay nearest to the orbital surface of the frontal lobe, i.e., nearest to the area in which his passionate and vituperative senior colleague Bouillaud said that speech lay (on both sides); and he chose the posterior part because that area was softened in his famous case "Tan Tan". But in "Tan Tan" there was also softening in the whole middle cerebral territory, including the upper and middle temporal, pre-central and post-central, and lower parietal convolutions, as Souques (1928) pointed out. It is not surprising that every kind of observation has failed to discover the real relationship of Broca's area to speech or even to certify with finality what part in speech the cortex of that area plays. It is quite clear that Broca's area was originally taken much too seriously; Broca's own observations were trivial. It is little more than the oddest of chances that the third left frontal convolution has anything to do with language. Broca knew nothing of its proximity to the not yet discovered face-head motor area.

Despite the labours of Sir Henry Head, Pierre Marie, Henschen, Wernicke, and others it cannot be said that we are much nearer an understanding of the physiological and cortical anatomical substratum of speech than we were many years ago. Stimulation of Broca's area in man may cause movements of the larynx and Penfield often produced crude vocalization without words by stimulation in the cortical head area, i.e., roughly in the posterior end of Broca's area. Stimulation in the pre-central area, but especially in the superior temporal and angular gyri, may lead to arrest of speech (Jefferson, 1935; Robb, 1948). Penfield's and my own excisions of Broca's area, with care to avoid deep undercuts in the white matter, have led at most to nothing more than transient aphasia.

The means by which our wordless sensa are turned into speech completely eludes us. Some, like myself, feel sure that the precursors of speech must surely be present in species lower than man; there are broad hints of this in anthropoids. It seems that an entirely new approach is required if we are to advance further. So far a new way has not been found. We are left with the belief that destruction of the angular gyrus leads to much more profound disturbances of ideation and language than do lesions elsewhere, and that they wreck mental processes more subtly than do severe frontal lesions. But physiology has as yet no new clarification of the underlying mechanisms to offer.

On the other hand, the somatotopic plan of the human post-central sensory area has advanced far since the first stimulation under local anaesthesia by van Valkenburg (1914) and by Cushing (1909). Thermionic recording from the post-central gyrus of animals (Bard, 1938) when sensory stimuli were applied to body and limbs has brought information of that area in these animals almost up to the level of our knowledge of it in man. It is interesting to note that local injections of strychnine into parts of the optic thalamus cause pain and paraesthesia in the animal very suggestive of Déjerine & Roussy's thalamic syndrome (1906). A more important discovery, unparalleled in the laboratory, has been the illuminating demonstration of the linkage between spatial orientation and the parietal cortex of both sides. A number of first-rate observations have been made on this type of agnosia by Holmes, Riddoch, Russell Brain, Critchley and Purdon Martin. The latter in particular has considered that man's spatial orientation depends on the lower parietal field.

Lesions in the parietal area have been shown to produce not only a loss of the power to find one's way about, even in the familiar purlieus of one's own house, but a loss of power to conceive space in even two dimensions. It becomes impossible to draw a plan of a house; for instance, the kitchen may be depicted as a separate disconnected object in the garden. The same lack of orientation holds for dressing if the plan of articles of clothing can no longer be perceived. Concurrently may be seen a loss of recognition of half the body as a personal property, as Purdon Martin (1949) illustrated. It is in such ways as these, as in the visual field analysis of occipital lesions, that the clinician has made contributions that could not have come either from experiments on animals or from purely histological studies. The map of cerebral function recently devised by Penfield (fig. 4) lacks reference to man's recognition of his personal orientation but otherwise is interesting.

6. Levels of Consciousness

The concept, that awareness of surroundings is a primitive defence mechanism in a wide biological sense and has a brain-stem location rather than a purely cortical one, was put forward by the present writer (Jefferson, 1943) in relation to concussion. This was not a complete innovation because Fulton and Bailey, J. C. White, and Penfield had produced evidence of extinction of consciousness by lesions in the region of the third ventricle. Cairns *et al.* (1941) had also described a state of "akinetic mutism" in a girl with a congenital pituitary cyst. None the less the notion of low-level location for consciousness seemed to shock the too "cortically minded". Clinical observation has, however, done nothing but confirm the view and it is doubtful indeed whether any cortical lesion can cause unconsciousness except by driving down to at least thalamic levels, as Penfield and Jasper have contended. Again, no one who has watched a clot in the posterior fossa causing a patient to go through exactly the same stages of increasing stupor as that caused by middle meningeal bleeding can fail to be impressed by the sensitivity of the brain-stem. This sensitivity shows itself not so much by alteration in the medullary vasomotor centre and respiratory centres but in extinction of consciousness, and that with normal or atmospheric pressure in the ventricles (Jefferson & Johnson, in press). The relevant area seems to be the upper pons and lower mid-brain, presumably by some suppression of afferents or effect on the upper brain-stem. In going to sleep, alterations in electrical rhythms are first seen in the thalamus and below, last of all in the cortex.

Bound up with these functions must be the integrative action of the thalamic reticular system and its relations with the brain-stem reticular systems recently disclosed by Jasper (1949). It is well known that cortical responses can be picked up in very circumscribed areas on stimulation of the dorso-medial nucleus of the thalamus, thus verifying physiologically the connecting fibres discovered by Le Gros Clark by anatomical methods of research. Exploration of the thalamus by stimulation along a fine insulated needle reveals a circumscribed point (which can be reached from several directions with the same result) at which control of the normal symmetrical cortical rhythms can be achieved. This area appears to be in the inter-laminar thalamic areas. It was known that the thalamus had a rhythm of its own of 8–12 per sec. waves, similar to the cortex, and some had thought that it was these thalamic rhythms which drove the cortex. Jasper, and Denis Williams working independently, did not accept this view; Williams' recent thalamograms confirm his belief (see Williams & Parsons-Smith, 1949). Jasper's experiments proved that the waves and, equally, bursts of activity, are not exactly synchronous in thalamus and cortex, though they could sometimes be in step. Stimulation of the thalamic reticular system caused a sudden stop of responsiveness in the freely moving conscious animal, suggesting an arrest of awareness as in petit mal. Powerful stimulation in the thalamus would cause a generalized fit. The important point is that stimulation of the thalamic reticular system had a wide-spread general effect on the animal's behaviour without affecting postural reflexes. After-discharge with slow spike and wave form was common. Magoun and his colleagues have brought forward evidence of the relationship between the reticular portion of the brain-stem and cerebral activity. Jasper (1949) concludes that there is in the thalamus a regulating mechanism "involving thalamic and other brain stem structures . . . controlling the form and rhythm of the background of cortical activity upon which afferent impulses must act, and regulating local and generalized excitatory states of the cortex as a whole." He believes that the thalamic reticular system is the most important item in these mechanisms. Whether these integrative actions will be confirmed by other writers and especially by thalamic stimulation in man remains to be seen.

These remarks on subcortical functions and their possible relationships to cortical control have been inserted in proof of something said in earlier passages: that we are in process of searching for some general scheme, however vague and uncertain its details might be, of the general plan of integration of the brain as an acting whole. My purpose has also been to show that the modern exploration of the cortex is deeply concerned with the physiological connexions of cortical areas to deeper structures. The search will be carried on in a vertical direction rather than on the plane surfaces of the cortical cartographers of 40 years ago. I do not intend to suggest that the cortical areas for long so well known are unimportant but that the integration is carried out not only by inter-cortical connexions but also by a multitude of "feed-backs" to the deeper structures of the brain, and that the physiological state of the cortex depends on the state of subcortical structures.

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ANATOMICAL RELATIONSHIPS BETWEEN THE CEREBRAL CORTEX AND THE HYPOTHALAMUS

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If the comparative anatomist were asked which parts of the cerebrum are to be regarded as the most primitive and archaic and which the most advanced and recently acquired (in the evolutionary sense), he would point to the hypothalamus and to the neopallial component of the cerebral cortex, respectively. The hypothalamus comprises a relatively well-developed part of the forebrain in all vertebrates, from the lowest to the highest and, indeed, shows but little change in its nuclear content and differentiation throughout an extensive comparative series which includes every level of mammalian development and even some of the submammalian vertebrates. The neopallial cortex, however, is commonly believed to have no representation in submammalian vertebrates, and, as is well recognized, undergoes a progressive elaboration in the evolutionary scale of the mammals until, in man, it achieves the acme of its development. This broad contrast, so apparent in comparative anatomical studies, is equally well reflected in physiological studies. On the one hand, the hypothalamus has been demonstrated to contain neural mechanisms intimately concerned with the regulation of autonomic functions and basic metabolic activities. On the other, the cortex provides the basis for such highly integrated functions as those concerned with sensory discrimination and the voluntary control of movement. It has, of course, been long accepted that these contrasting aspects of cerebral function are by no means wholly independent of each other. But it is probably fair to say that for many years neurologists have tended to assume that, within the organization of the cerebrum as a whole, these functions have become segregated to the extent that functional interrelationships between them occur predominantly at lower levels.

Undoubtedly one of the outstanding features of the study of brain functions during recent years is the demonstration that the interaction of cortical and hypothalamic functions is much more direct than had been supposed. For example, impulses from important centres in the hypothalamus can be directly projected, through monosynaptic relays, to specific areas of the cortex, while electrical stimulation of these specific areas of the cortex can be shown to affect autonomic activities through the medium of the hypothalamus. Apart, however, from the evidence of specific relationships between hypothalamic nuclei and cortical areas, there is also evidence that the hypothalamus may profoundly influence the activity of the cortex as a whole. Thus the spontaneous rhythmic electrical activity of widespread areas of the cerebral cortex may be modified or abolished by appropriate lesions in the hypothalamus (Obrador, 1943), while electrical stimulation of the hypothalamus may accentuate cortical potentials (Grinker & Serota, 1938). It now appears certain that the hypothalamus influences the cerebral cortex through the intermediary of certain principal nuclei of the thalamus which project on to focal areas of the cortex. In recent years it has also been shown that other elements of the thalamus, represented by the intralaminar and mid-line nuclei, have a diffuse projection by means of which the rhythmic activity of extensive areas of the cortex may be controlled and integrated; this raises the interesting question whether these elements may perhaps also serve to relay hypothalamic impulses of a more generalized type.

In any case, it is clearly a matter of some importance to determine to what extent cortical functions, whether expressed in focal responses or in total patterns of rhythmic activity, may be ultimately determined, or at least influenced, by activation from primarily hypothalamic sources, and it is partly for this reason that more and more attention has been focused in recent years on the precise details of cortico-hypothalamic fibre connexions. In this short review, we are concerned to give a précis of our present knowledge of these connexions and to indicate the methods which may be used to elucidate them in still further detail.

1. Afferent Hypothalamo-Cortical Connexions

Apart from the possibility of diffuse and indirect ascending connexions, through which impulses from the hypothalamus may eventually be relayed to the neopallial cortex, there are now known to be two main relay centres in the thalamus whereby such impulses are focused directly on to specific cortical areas. These centres are the anterior nucleus and the dorsomedial nucleus.

a. Anterior Nucleus

The anterior nucleus of the thalamus in lower mammals can be readily subdivided into three quite distinct elements, the anterodorsal, anteroventral and anteromedial nuclei, and the earlier evidence that these three elements project on to specifically different areas of the so-called limbic cortex has now been confirmed in considerable detail by Rose & Woolsey (1948). In the higher primates, including man, the anteromedial element has undergone retrogression, and the main element is the anteroventral. This well-defined group of cells is sufficiently large in the human brain to form a conspicuous eminence—the "anterior tubercle"—on the upper surface of the thalamus, which every student sees for himself when he first dissects a brain.

The anteromedial element of the anterior nucleus is connected with the anterior limbic region (area 24),[1] the anteroventral element sends its fibres to the posterior limbic region, at least mainly to area 23, while the smaller anterodorsal element projects still further back to the retrosplenial region of the cortex. In the human brain the main element of the anterior nucleus probably sends some fibres to area 24 (as well as to area 23), and it may be, therefore, that it represents a mergence of the anteroventral nucleus with remnants of the anteromedial element of lower mammals. Since the anterior nucleus of the thalamus is known to receive its afferent impulses by way of the mamillo-thalamic tract (bundle of Vicq D'Azyr) which, again, takes origin from the mamillary body (mainly the medial mamillary nucleus), it evidently serves as a simple relay whereby the mamillary component of the hypothalamus acquires a cortical representation. The significance of this very well-defined projection system is by no means certain. For many years it has been ignored and forgotten, on the assumption that it was an unimportant relic of the " rhinencephalon ". Until quite recently, indeed, standard textbooks have mistakenly included the whole of the limbic cortex, as well as the mamillary body, the bundle of Vicq D'Azyr and the anterior thalamic nucleus, in the " rhinencephalon ". It is clear that the term " rhinencephalon " has led to very serious misconceptions, and it should now be redefined. The reason for attributing olfactory functions to this system was simply that the mamillary body is the terminal station of the fornix system which has its main origin in the hippocampus, and the latter had come to be regarded as " olfactory cortex ". In recent years, however, increasing doubt has been thrown on this traditional conception, and the critical review by Brodal (1947), as well as the more precise definition of the olfactory pathways and centres in the rabbit (Le Gros Clark & M. Meyer, 1947) and monkey (M. Meyer & Allison, 1949), has made it clear that this view can no longer be seriously maintained.

This being so, it now becomes a matter of the greatest importance to elucidate the real functional significance of the hippocampus. Unfortunately, little is known of the details of its afferent connexions, except that at least the majority of them come from the posterior piriform cortex and from the cortex of the limbic region (either directly or by way of the cingulum). This latter connexion provides anatomical evidence for the supposition that the hippocampus and the fornix system form part of a circuit which perhaps maintains a continuous cycle of functional relationship between the hypothalamus and the neopallial cortex. This circuit, it seems, would be made up as follows: hippocampus⟶fornix⟶mamillary body⟶anterior nucleus⟶limbic cortex⟶cingulum⟶hippocampus. It is by no means, however, a closed circuit. For example, although the mamillary body is mainly served in its afferent connexions by the fornix and hippocampus, its cells may also be influenced through ascending fibres which are present in the mamillary peduncle (Ibañez, 1938) and probably have their origin in the ventral tegmental nucleus of the midbrain (Fox, 1941); in addition the cells are almost certainly influenced by impulses from adjacent parts of the hypothalamus, and also by corticofugal fibres derived (at least in part) from area 6 of the frontal lobe (*vide infra*). Again, impulses from the anterior nucleus of the thalamus which arrive at the limbic cortex may presumably be influenced there by the activity of other areas of the cortex. Nevertheless, the circuit appears to be exceedingly well defined anatomically and it is all the more remarkable, therefore, that its function should still remain so obscure. Possibly it plays a part in maintaining neopallial activity (either by activation or inhibition) at a level necessary for the manifestation of normal cortical functions during waking life. In this connexion, it is worth bearing in mind that the cingulate gyrus of the limbic cortex forms one of the " suppressor areas " and, like all the other suppressor areas of the cerebral cortex, pours efferent association fibres into the mysterious area 32 which A. Meyer & McLardy (1949) have referred to as a nodal point of considerable physiological activity between cortex and subcortical basal ganglia. That it has some concern with cortical activities underlying rather complex psychological processes is suggested by the few observations which have so far been made on the clinical effects of interference with some parts of the circuit (see, for example, Grünthal's report of a case with circumscribed destruction of the corpora mamillaria, 1939). On the other hand, so far as physiological responses of a simple type are concerned, experimental investigations involving the circuit in animals have so far led to little result, apart from the fact that stimulation of the anterior limbic area has been shown to lead to autonomic and motor phenomena (Smith, 1945; Ward, 1948). Sigrist (1945), who made a careful study in Hess's laboratory of the effect of stimulation of the mamillo-thalamic tract in the cat, was forced to conclude that there is no definite physiological response which can be related to it (" . . . derselbe muss daher für den Tierversuch als ' stumme Zone ' angesehen werden ").

It is of some interest to note that the hippocampal circuit referred to above is characteristic of the mammalian brain; it appears to have no representation in the reptilian brain. Thus, in spite of statements which have sometimes been made to the contrary, there is nothing in the reptilian brain which corresponds to the medial mamillary nucleus, the mamillothalamic tract, or the anterior nucleus of the thalamus (see Ariëns Kappers' study of the mammalian homologues of the dorsal thalamic nuclei of reptiles, 1942). It follows that the functions subserved by the circuit must have a relation to forms of cerebral activity which are not to be found in any vertebrates other than mammals. In other words, it is hardly likely to be concerned with physiological responses of an elementary character.

b. Dorsomedial Nucleus

We may now briefly refer to the other main element of the thalamus concerned with the relay to the neopallial cortex of impulses originating in the hypothalamus, viz., the dorsomedial nucleus (medial nucleus of human anatomical terminology). The fact that this nucleus projects mainly on to the granular areas of the frontal lobe has now been amply confirmed by many investigators, and the relation of different sectors of the nucleus to specific cortical areas has been studied in great detail in leucotomized human brains by A. Meyer, Beck & McLardy (1947). These authors have shown, *inter alia*, that the medial portion of the dorsomedial nucleus (which is in most immediate relation to the periventricular system of fibres in the wall of the third ventricle) projects on to the orbital cortex, while the main lateral part sends fibres

[1] Except where otherwise stated, the numbers refer to the areas of the cortex in Brodmann's notation (cf. fig. 1 in article by Jefferson, p. 334).—Ed.

to areas on the convexity of the frontal lobe. That these fibre connexions with the cortex serve to relay hypothalamic impulses was initially inferred from anatomical evidence (not entirely satisfactory) that the hypothalamus is linked with the dorsomedial nucleus by the periventricular system of fibres which ascend close to the wall of the third ventricle. This has now received confirmation from the electro-physiological studies of Murphy & Gellhorn (1945), who were able to demonstrate characteristic changes in electrical potentials in the dorsomedial nucleus following strychninization of the posterior hypothalamus. Incidentally, they adduced evidence that impulses may also pass in the opposite direction —from the dorsomedial nucleus to the hypothalamus. Thus, since it has been well established on anatomical evidence that cortico-thalamic fibres connect the frontal areas with the dorsomedial nucleus, it is evident that hypothalamic activities may be indirectly influenced by the cerebral cortex through this pathway.

The nature of the impulses which are conveyed from the hypothalamus to the frontal cortex is not known, but evidence has accrued from the study of leucotomy cases that interruption of the projection fibre system from the dorsomedial nucleus can be to some degree correlated with the personality changes observed after this operation (see, in particular, the careful studies of A. Meyer & McLardy, 1949). It has also been reported by Spiegel *et al.* (1947) that bilateral lesions made surgically in the dorsomedial nuclei of the thalamus (as a substitute for frontal leucotomy) produce personality changes of a similar type. These observations are in harmony with those made previously on the association of mental deterioration with pathological affections involving the dorsomedial nuclei and periventricular system (Smyth & Stern, 1938), and may also be related to the well-known correlation between hypothalamic lesions and gross disturbances of emotional behaviour (see A. Meyer, 1944).

The anatomical details of the conducting system represented by the hypothalamus⟶dorsomedial nucleus⟶ frontal cortex connexions are now fairly well known so far as the thalamo-cortical relationships are concerned. But they are still far from complete in regard to the hypothalamo-thalamic relationships. As already noted, the work of Murphy and Gellhorn indicates that impulses reach the dorsomedial nucleus from the posterior hypothalamus, but we do not yet know from which particular nuclear elements in this region. This is a problem which urgently needs elucidation by experimental anatomical methods.

Like the anterior nucleus, the dorsomedial nucleus of the thalamus has no representation in vertebrates other than mammals, and on these grounds alone may be presumed to subserve some of the more elaborate mental processes which depend on cortical activity. It appears to be present in all grades of mammals, but in primitive mammals the cortical area at the frontal pole of the cerebral hemisphere to which it projects is relatively very small (see Rose & Woolsey, 1947).

2. Efferent Cortico-Hypothalamic Connexions

We now come to a consideration of the anatomical pathways whereby cortical activities are enabled directly to influence hypothalamic functions—a problem of particular interest, since such pathways presumably form (at least in part) the basis for the apparently causal relationship which has been noted to exist between higher mental processes and autonomic activities. In recent years the increasing accumulation of evidence has tended to emphasize the association of autonomic functions with certain specific regions of the frontal cortex. A review of this evidence also makes it apparent that, apart from the cingulate gyrus, there are two focal regions of what may be termed " autonomic representation " in the frontal lobe, one lying between the motor cortex and the frontal granular areas (the " cortico-autonomic belt " of Kennard, 1944), and the other on the orbital surface of the frontal lobe. This experimental evidence finds some confirmation from the clinical study of leucotomized patients, for it has been demonstrated that the more-posteriorly situated cuts in leucotomy (that is to say, involving the pre-motor and posterior orbital regions) are likely to be followed by autonomic disturbances (A. Meyer & McLardy, 1949). On the other hand, very few of these undesirable effects occur after strictly " prefrontal cuts ".

a. Fronto-Hypothalamic Connexions

It has been recognized for some time that indirect pathways exist in the brain whereby impulses from the frontal lobe can be indirectly relayed to the hypothalamus through the septal and pre-optic regions, or the subthalamus. The first demonstration of *direct* fronto-hypothalamic connexions was made by Ward & McCulloch (1947), using the method of physiological neuronography. These authors mapped out descending connexions from certain specific areas of the frontal cortex (in particular the pre-motor and orbital regions) to certain specific nuclei of the hypothalamus, suggesting an elaborately organized pattern of connexions between these two functionally contrasted levels of the brain. By their technique, they traced cortico-hypothalamic fibres to the lateral and posterior hypothalamic areas, the mamillary body, and the supra-optic and paraventricular nuclei. The further study of these connexions is now being undertaken by direct anatomical methods in the Department of Anatomy at the University of Oxford, in order to define with greater certainty their precise distribution. These methods involve the ablation of specific areas of the cortex in macaque monkeys, and the study of the resulting terminal degeneration of cortico-fugal fibre systems a few days later with Glees' silver technique. The detailed results of these studies will be published elsewhere, but it is appropriate to summarize here some of the observations in relation to their possible functional implications.

One of the most interesting results of the degeneration experiments which we have been carrying out in the monkey is the demonstration of quite a massive projection of direct cortico-hypothalamic fibres from the postorbital cortex (an area practically equivalent to Walker's area 13), and also from the pre-motor cortex (area 6), to the ventromedial hypothalamic nucleus. This connexion is bilateral, the heterolateral fibres crossing in the rostrum of the corpus callosum, and passing through the pre-optic region in close association with the descending column of the fornix. It also appears probable that on both sides the fibres are finally conveyed to their termination by way of the medial forebrain bundle. The ventromedial hypothalamic nucleus, it should be noted, lies in the pars tuberalis of the hypothalamus, and its topographical position (or, at any rate, that of the adjacent part of the medial forebrain bundle through which afferent

fibres reach it) appears to correspond fairly closely with Hess's " intermediate zone of the hypothalamus ", which this authority showed to respond to electrical stimulation by a complex syndrome of sympathetic discharge (Hess, Brügger & Bucher, 1946). A similar effect was noted by Wheatley (1944), who correlated the development of a type of " sham rage " with injuries localized to the ventromedial nucleus. Also apposite to these observations are those of Sachs, Brendler & Fulton (1949) who reported that, following the application of strychnine to the posterior orbital cortex, pronounced potential changes could be recorded in the region of the medial forebrain bundle in the hypothalamus. It is interesting to note that some of the autonomic effects which follow stimulation of this region of the hypothalamus may also be elicited by stimulating those areas from which the ventromedial hypothalamic nucleus mainly receives its cortical connexions, i.e. the posterior orbital cortex and the pre-motor cortex (see, for example, Bailey & Sweet, 1940; Delgado & Livingston, 1948; Kennard, 1944). According to our experimental anatomical studies, these cortical areas also send fibres, either directly or by collaterals, to the anterior hypothalamic area, the dorsomedial hypothalamic nucleus, and the periventricular arcuate nucleus, but these connexions are by no means so numerous as those which reach the ventromedial hypothalamic nucleus.

The demonstration of rather abundant cortical connexions with the ventromedial nucleus of the hypothalamus, and the physiological evidence that autonomic responses of various kinds may be obtained by electrical stimulation in this region, suggest that this hypothalamic element represents an important focal area for a number of fibre systems concerned with the control of autonomic functions. It is therefore of some interest to note that, in the human foetal brain, the ventromedial nucleus develops precociously and for a time appears as a relatively large and very circumscribed group of cells (Le Gros Clark, 1938). Later on in foetal development its outline becomes more diffuse and thus not so easily definable, probably in relation to the increasing complexity of its fibre connexions with adjacent regions of the hypothalamus and with more distant parts of the brain by way of the medial forebrain bundle.

So far, we have not been able with certainty to demonstrate anatomically any direct cortical connexions with the paraventricular and supra-optic nuclei (though these must be presumed to be present from the electrophysiological studies of Ward and McCulloch). The importance of such connexions has reference to the fact that these nuclei are closely linked by efferent fibres with the neurohypophysis, and a pathway is thus provided whereby pituitary functions may be influenced rather directly by the cortical activities of the frontal lobe.

b. Connexions between Frontal Cortex and Mamillary Body

Anatomical evidence for a direct fibre path from the frontal cortex to the mamillary body has been provided by the detailed study of brains which have been subjected to leucotomy operations (M. Meyer, 1949). From this evidence it appears that these fibres are mainly derived from the pre-motor cortex (area 6), and no doubt correspond to the connexions inferred by Ward and McCulloch to have their origin in the corresponding area (6a) in the monkey's brain. The cortico-mamillary fibres terminate mainly in the caudal part of the main or medial mamillary nucleus, and it seems probable that they reach their objective by passing through the internal capsule and traversing the subthalamic area. The function of this system is not known, for the reason, already noted, that nothing is really known of the functional significance of the mamillary body.

c. Limbic Cortex and Hippocampus

We have made mention of two main efferent systems linking the neopallial cortex directly with the hypothalamus. Another efferent system, less direct, is of course that represented by the limbic cortex and hippocampus to which reference has already been made. From our experiments on the monkey brain, using the method of terminal degeneration, it is clear that efferent fibres extend back from the gyrus cinguli (area 24) to the retrosplenial areas of cortex, and there is good reason to suppose that these areas in their turn supply afferent fibres to the hippocampus from which the fornix system mainly arises. But there is evidence that a small proportion of the fibres of the fornix take their origin directly from the limbic cortex, and the latter is thereby brought into much more direct relationship with the mamillary body. Further experimental studies in our laboratory (Sprague & M. Meyer, 1950) have recently made it evident that, in the rabbit, the fornix terminates mainly in the basal and intermediate parts of the medial mamillary nucleus. None appears to reach the lateral nucleus. It should be noted, also, that some fibres of the fornix definitely leave the main fascicle to end in the septal region (and possibly the anterior hypothalamus), while others extend back beyond the mamillary body towards the tegmental region of the midbrain. Lastly, contrary to the usual textbook description, it has not been found possible to detect any contribution from the fornix to the habenular region by way of the stria medullaris.

3. Conclusion

The more or less direct anatomical connexions between the neopallial cortex and the hypothalamus which we have briefly described in this review are those which have now been defined with considerable certainty by anatomical or electrophysiological methods. Taken by themselves, they evidently betoken a much closer functional relationship between these contrasting levels of cerebral organization than might have been supposed a few years ago. In conjunction with the evidence of physiological experimentation, they also make it clear that there are certain topographical regions of the cerebral cortex which are specifically concerned with this relationship, in the sense that they are more intimately connected than other areas with autonomic effector mechanisms in the hypothalamus. The importance of these relationships seems clear, for they evidently provide for the integration of primitive autonomic mechanisms (such as are associated, for example, with instinctive urges and emotional reactions) with neural activities taking place at the highest functional levels of the brain. It is not surprising, therefore, that interference with this system should lead to psychological disturbances affecting the very structure of what is usually termed " personality ". No doubt it is still far from clear precisely what part is played in these high-level integrations by the anatomical connexions to which we have referred. But clinical and

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THE HYPOTHALAMUS AND ENDOCRINE GLANDS

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1 Adrenal medulla and neurohypophysis
  a Adrenal medulla
  b Supraoptico-hypophysial tract
  c Secretion of antidiuretic hormone
2 Adenohypophysis and the gonads, thyroid and adrenal cortex
  a Mode of transmission of stimuli
  b Effect of sectioning pituitary stalk
  c Secretion of adrenocorticotrophic hormone
3 Conclusion
References

The internal environment of the body is controlled by the autonomic nervous system and by humoral means. It seems likely that adjustments of the internal milieu mediated by these two mechanisms are integrated in the hypothalamus. Hypothalamic control of the autonomic nervous system has been the subject of intense study. Following the pioneer work of Karplus and Kriedl, many schools took up this field of investigation with particular regard to the quicker reactions concerned with the control of the blood-pressure, respiration, body temperature and similar functions. This aspect of hypothalamic physiology has been ably summarized in many reviews (Ranson & Magoun, 1939; Ranson, 1940; Miller, 1942; Hess, Brügger & Bucher, 1945–6). However, hypothalamic control of humoral mechanisms such as the slower metabolic and endocrine processes has received much less attention, and it may be said that little is known of the interrelation between the central nervous system and the ductless glands. Except for the adrenal medulla and the neurohypophysis (posterior pituitary gland), the position of endocrinology today may be likened to that of the vascular system if the function of vagus and sympathetic nerves were as yet undiscovered. That the reproductive and other endocrine functions are brought into harmony with the external environment and general somatic requirements is well established, but the investigation of the mechanism whereby such co-ordination is brought about is only in its opening phases. This review deals with such work.

1. Adrenal Medulla and Neurohypophysis

These two glands are exceptional in the endocrine series in that they are closely associated with the central nervous system in development, being derived from neural crest material and from the diencephalon, and both are dependent on a rich nerve supply for normal function throughout life.

a. Adrenal Medulla

The adrenal medulla is supplied by the splanchnic nerves and by the upper lumbar sympathetic chain (Swinyard, 1937; Young, 1939), and if these nerves are cut it is doubtful whether the gland continues secreting. It certainly becomes inexcitable to electrical stimuli that elicit secretion in the normal gland (Cannon & Rosenbleuth, 1937). Houssay & Molinelli (1925), using a crossed circulation technique, showed that stimulation of the infundibular region of the hypothalamus elicits secretion by the adrenal medulla in dogs, which is abolished by section of the great splanchnic nerve. Magoun, Ranson & Hetherington (1937) likewise found that stimulation of the hypothalamus resulted in release of adrenin into the circulation, the loci active to stimulation being situated

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experimental enquiries are beginning to demonstrate how important they may be, and it seems to us that these enquiries may be considerably facilitated in the future if those who pursue them are made familiar with the essential anatomical data concerned. This, indeed, is the main reason why we have prepared this short review.

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in the anteroposterior extent of the lateral hypothalamic area and the adjacent perifornical region. It would seem clear from this and other evidence that the hypothalamus influences adrenaline secretion, as part of general sympathetic control, by means of a pathway through the brain stem, spinal cord and splanchnic nerves; and that in the hypothalamus the activity of the adrenal medulla is co-ordinated with the requirements of the organism under varying patterns of emotional excitement.

b. Supraoptico-Hypophysial Tract

The neurohypophysis is innervated by a very rich tract of unmyelinated fibres descending to the gland in the neural stalk. These fibres originate mainly in the supraoptic nucleus, some in the paraventricular nucleus and possibly other hypothalamic nuclei (for discussion, see Harris, 1948a). Functionally, the most important tract appears to be the supraoptico-hypophysial (SOH) tract, as first shown by the classical work of Ranson and his colleagues (Fisher, Ingram & Ranson, 1938). These workers found that bilateral lesions of this tract were followed by loss of secretory activity of the neurohypophysis with a resultant state of diabetes insipidus, by degeneration and atrophy of the neurohypophysis and of the supraoptic nucleus, and by a loss of active material (antidiuretic, oxytocic and pressor) extractable from the glands. For the first time the relationship between the hypothalamus and pituitary gland and the water balance of the body, and the analysis of clinical cases of diabetes insipidus, were on a sound basis. The effect of similar lesions on the oxytocic activity of the gland and the mechanism of parturition is not clear cut. Fisher, Magoun & Ranson (1938) and Dey, Fisher & Ranson (1941) found that lesions of the SOH tract in cats and guinea-pigs were followed by dystocia in a high proportion of cases, though some animals that exhibited a state of diabetes insipidus delivered their young normally. It has been reported that clinical cases of diabetes insipidus may suffer from dystocia (Marañón, 1947), and the position has been discussed (Harris, 1948b).

The converse experiments, electrical stimulation of the SOH tract with resultant positive responses from the neurohypophysis, have been technically difficult to perform, since anaesthesia itself tends to inhibit water diuresis, against the background of which the antidiuretic effect is observed. However, Haterius (1940), Haterius & Ferguson (1938) and Ferguson (1941) made the experiment in anaesthetized rabbits and cats and obtained evidence that electrical stimulation of the pituitary stalk causes secretion of the antidiuretic and oxytocic hormones. The experimental procedure was much simplified when remote control stimulation was applied to the hypothalamic region and it became possible to stimulate different regions without the use of an anaesthetic. In a preliminary operation a small coil was buried between the scalp and skull of a rabbit and an insulated electrode carried down through the skull, corpus callosum and other median structures into some part of the hypothalamus or pituitary gland. After recovery from the initial operation, stimulation could be performed in the conscious state by placing the animal with its head in an electro-magnetic field. Using this method it was found that localized stimulation of the SOH tract produced secretion by the neurohypophysis and, as a result, the following reactions occurred—inhibition of a water diuresis; an increase in the relative, and sometimes absolute, urinary chloride; a marked increase in uterine activity in the oestrous, or oestrogenized rabbit, but no increase in the pseudopregnant animal or animal treated with progesterone; an increase in intestinal activity; only slight rises in blood-pressure of the same type as those produced by injection of posterior pituitary extract; no increase in blood-sugar; and the appearance of an antidiuretic substance in the urine (Harris, 1944 (thesis for M.D. degree, Cambridge University); 1947a, 1948d, 1948e). It is of interest that the secretion produced by stimulation of the SOH tract appears to possess relatively more oxytocic than pressor activity as compared with standard posterior pituitary extracts. For example, maximal stimulation of the tract for 1 min. causes the secretion of the equivalent of 200–500 mU oxytocic factor and less than 100 mU pressor factor. The fact that the rabbit possesses a mechanism for increasing the activity of the empty oestrous uterus may be significant in relation to sperm transportation during and after coitus (Harris, 1948f).

c. Secretion of Antidiuretic Hormone

The changes in the external environment and internal milieu which in the normal animal elicit secretion of the antidiuretic hormone, and the mechanism whereby such changes affect the neurohypophysis, have been the subject of a series of investigations by Verney and his colleagues. Their work has firmly established the posterior pituitary antidiuretic secretion as a true hormone. Rydin & Verney (1938) investigated the inhibition of a water diuresis produced by muscular exercise. They found the inhibiting factor was the emotional accompaniment of the exercise, and showed that the effect of emotion was not mediated by the nerve supply of the kidney, or by the participation of haemodynamic factors. They suggested that the antidiuretic effect of emotion was humorally conducted to the kidney, and they produced strong indirect evidence that the humoral agent was the pituitary antidiuretic hormone. O'Connor & Verney (1942) then found that removal of the posterior pituitary gland in dogs reduced the emotional inhibition of a water diuresis to 5 per cent of its original magnitude. Section of the SOH tract (O'Connor, 1946) also very largely abolished the emotional inhibition of a diuresis. Much of this work was performed on dogs in which the kidneys and adrenals had been denervated.

In further work, on dogs with intact sympathetic systems, O'Connor & Verney (1945) distinguished a second type of emotional inhibition of a diuresis. The inhibition of pituitary origin is slow and prolonged, but this second type was rapid in onset and evanescent in duration. After denervation of the adrenal glands and kidneys, a long slow inhibition was apparent in all cases. It did appear, then, that an intact sympathetic system may prevent the development of an inhibition of pituitary origin. It was then found that injection of adrenaline immediately prior to an emotional stress stimulus likewise prevented any pituitary-type inhibition of a water diuresis, although adrenaline did not prevent an inhibition following the injection of posterior pituitary extract. Further work (Verney, 1947) showed that tyramine acts in a similar manner to adrenaline, and it is thought that the most likely mode of action is through interference with the chemical reactions initiated in the nervous system by the emotional stress stimulus. Attention was then turned (Verney, 1946, 1947) to the effect of changing the osmotic pressure of the blood on the secretion of the antidiuretic hormone by the posterior pituitary gland. It was found that intracarotid injections of hypertonic sodium chloride over a 5–20 sec. period caused a

release of antidiuretic hormone with resultant inhibition of a water diuresis, the response being diminished by some 90 per cent after removal of the posterior lobe. This response was shown to be osmotically determined, the receptive elements being situated somewhere in the vascular bed of the internal carotid artery. The osmoreceptors were shown to be freely permeable to urea, less freely permeable to dextrose, and relatively impermeable to sodium chloride and sucrose. A local increase in osmotic pressure of only 2 per cent (in experiments involving intracarotid infusions lasting 40 min.) was found to cause an antidiuresis which had a postpituitary extract equivalence of 1μU/sec. The change in blood-chlorides in these latter experiments is within the range of changes found physiologically in man. It would seem likely that the osmoreceptors postulated by Verney lie within the supraoptic nucleus of the hypothalamus. This nucleus possesses an exceedingly rich blood supply, which is a likely attribute of a chemoreceptor, but there is as yet no proof that it is the location of the receptive structure.

Since emotional stress excites the secretion of the antidiuretic hormone it would seem probable that the supraoptic nucleus is in turn excited by afferent nerve tracts from other regions. There is evidence that these tracts are cholinergic in nature. Pickford (1939) showed that intravenous injection of acetylcholine into the dog inhibited a water diuresis, but that the inhibitory effect could not be produced after removal of the posterior pituitary gland. Burn, Truelove & Burn (1945) found that nicotine had a similar action in man. These experiments did not definitely localize the site of action of acetylcholine or nicotine as being in the supraoptic nucleus, but Pickford (1947) has further shown that injections of 0·004 cm.^{3} (totalling from 2 to 40 μg.) of acetylcholine solution directly into the supraoptic nucleus of chloralosed dogs interrupts the course of a water diuresis. Further interesting work by Pickford and her colleagues (personal communication, 1949) has disclosed that injection of di-isopropylfluorophosphonate (DFP), an inhibitor of cholinesterase, into the supraoptic nuclei of chloralosed diuretic dogs results in an immediate inhibition of the water diuresis, followed by a delayed effect in which marked polyuria and polydipsia occur and persist for 4–9 days.

Summarizing the evidence concerning hypothalamic control of the neurohypophysis, it may be said that anatomically the neurohypophysis has a rich innervation from the supraoptic nucleus; that lesions of the supraoptico-hypophysial tract produce diabetes insipidus and atrophy of the neurohypophysis; that stimulation of the tract causes secretion of the antidiuretic (pressor) and oxytocic factors; that the supraoptic nucleus is stimulated (either directly or indirectly) by changes in the osmotic pressure of the blood, and by cholinergic nerve tracts from other regions of the brain subserving emotional and possibly other reactions.

2. Adenohypophysis and the Gonads, Thyroid and Adrenal Cortex

The crucial problem in endocrinology at the present time is the inter-relationship between the central nervous system and the anterior pituitary gland, gonads, thyroid and adrenal cortex. It is beyond doubt that neural processes influence the internal secretion of these glands, and that the hormones liberated react back on the nervous system, so producing profound behaviour changes; but the mechanisms involved are largely conjectural.

There is much evidence that the anterior lobe of the pituitary gland is under the influence of the nervous system and that, through the eutrophic pituitary hormones, the gonads, thyroid and adrenal cortex are brought indirectly under neural control (see Harris, 1948a). As examples of such an influence may be quoted: (i) the important observations of Marshall (1922, 1936, 1942) on the effect of the external environment on reproductive processes; (ii) the fact that small localized tumours in the region of the tuber cinereum may produce precocious puberty in young children (Weinberger & Grant, 1941); (iii) the well-known disturbances that may occur in the menstrual rhythm or in the process of lactation due to psychological disturbances such as worry, fright, hypnosis; (iv) the effect of the environmental temperature on thyroid histology (Uotila, 1939; Brolin, 1945); and (v) the effect of emotional and other types of stress on the histology and activity of the adrenal cortex (Sayers & Sayers, 1948). It seems highly probable that these effects are produced by means of the hypothalamo-adenohypophysial system.

a. Mode of Transmission of Stimuli

The anatomical pathway by which the hypothalamus influences anterior pituitary secretion has been the subject of much debate. Most workers have found, on microscopic examination, that the anterior pituitary gland possesses a scanty nerve supply. These findings, and the fact that the anterior pituitary gland possesses a rich reticular fibre framework which may stain by silver methods to give the appearance of nerve fibres, put the onus of proof on those authorities who claim to have found many nerve fibres in the gland. Such claims now need the substantiation of two control procedures: firstly, to stain alternate sections for nerve fibres and reticular fibres and compare the fibre patterns disclosed; and secondly, to stain simultaneously sections from a normal gland and a "denervated" gland (after cervical sympathectomy and pituitary stalk section), in order to demonstrate the presence of nerve fibres in the normal gland, and the absence in the "denervated" gland. At the present time, it may be said that there is no convincing histological evidence of secretory nerves in the pars distalis of the adenohypophysis.

The same conclusion may be drawn from the experimental evidence available. Three nervous pathways have been suggested as possible routes for hypothalamic control of the anterior pituitary: the cervical sympathetic system, the parasympathetic fibres of the petrosal nerves, and the hypothalamo-hypophysial tract in the pituitary stalk. Section of these various nerves, however, does not necessarily prevent neural processes from affecting anterior pituitary secretion.

Apart from the nerve tracts mentioned above, another anatomical pathway exists connecting the median eminence of the tuber cinereum and the anterior pituitary gland. Rainer of Bucharest noticed, in human autopsy material, blood-vessels running longitudinally along the pituitary stalk. One of Rainer's pupils, Popa, working in collaboration with Fielding, first described these vessels in detail (Popa & Fielding, 1930, 1933). On histological grounds they claimed that blood was collected from the sinusoids of both lobes of the pituitary, carried upwards in large vascular trunks along the pituitary stalk, and redistributed by a secondary net of capillaries in the hypothalamus. For this reason the authors

termed the vessels "hypothalamo-hypophysial portal vessels". Wislocki & King (1936) and Wislocki (1937, 1938) confirmed the presence of these vessels, but differed from Popa & Fielding in claiming that the vessels started in the median eminence of the tuber cinereum, that the direction of flow was from above downwards, and that the vessels ended entirely in the pars distalis of the pituitary. Since the median eminence is, strictly speaking, part of the neurohypophysis rather than of the hypothalamus, the vessels were renamed the "hypophysial portal vessels". Green & Harris (1947) re-investigated the region in a variety of mammals and largely confirmed the findings of Wislocki. They found that small arterial twigs, branches of the internal carotid or posterior communicating arteries, run to supply a large vascular plexus situated between the pars tuberalis and median eminence. From this plexus arises a multitude of wide capillary loops which penetrate into the tissue of the median eminence where they come into intimate relationship with the nerve fibres of the hypothalamo-hypophysial tract. The blood from these loops is drained by means of large portal trunks running in the pars tuberalis envelope of the neural stalk, these trunks breaking up and redistributing the blood into the sinusoids of the pars distalis. The exact pattern of these vessels varies in detail in different mammals. In animals with short pituitary stalks, such as the dog, the intermediate trunks of the portal vessels may be likewise short and the two terminal sets of capillaries approximated, but in forms where the stalk is elongated, as in man, the portal trunks are also long. Green (1947, 1948, 1949; personal communication, 1949) has recently made a thorough investigation of the portal vessels in many types of vertebrates and finds a similar system of vessels in all forms examined from the Salientia to the Primates. Even in the porpoise and the whale (forms in which the anterior and posterior lobes of the pituitary gland are separated by a septum of thick connective tissue) a well-marked portal system of vessels is present and connects the median eminence and pars distalis by passing anterior to the septum (Harris, 1947b; unpublished observations, 1949). It has been suggested that, embryologically, the portal vessels are related to the lateral lobes of Rathke's pouch; and the significance of the pars tuberalis, which is derived from the lateral lobes, lies in the fact that it forms a bed for the vascular pathway between the nervous system and pars distalis (Harris, 1947c). The direction of blood-flow in the portal vessels has been a subject of much controversy. Direct microscopic examination of the vessels in living amphibians (Green, 1947) and rats (Green & Harris, 1949) has established that the blood flows from the median eminence to the pars distalis of the pituitary. To complete this summary of the blood-vessels of the gland, it may be added that, besides a portal system of supply, the pituitary receives a systemic arterial supply by means of branches from the internal carotid artery, and that the venous drainage is by wide veins which pass laterally into the adjacent venous sinuses.

In view of the above anatomical facts it was suggested (Harris, thesis, 1944; Green & Harris, 1947) that the hypothalamus may influence the secretion of the adenohypophysis by means of a neurovascular link, viz., that hypothalamic nerve fibres end in close relation to the capillary loops in the median eminence and, on excitation, liberate some chemo-transmitter into these vessels, this substance being transported by the portal vessels to excite or inhibit the pars distalis of the gland. It may be said that the experimental evidence available lends strong indirect support to the theory of neurovascular transmission of stimuli.

b. Effect of Sectioning Pituitary Stalk

Very varied effects have been recorded by different workers after sectioning the pituitary stalk. To take one example, the effect of pituitary stalk section on the oestrous cycles and reproductive processes in rats has been studied in detail. Following this operation, Richter (1933) found that oestrous cycles were prolonged, Westman & Jacobsohn (1938a, 1938b), and Brolin (1945) reported gonadal atrophy, whilst, on the other hand, Dempsey & Uotila (1940) and Dempsey & Searles (1943) found that some animals showed normal reproductive processes. Similarly, diverse results have been reported by workers who have studied the effects of stalk section on other pituitary functions such as lactation, maintenance of the thyroid and adrenal glands, and carbohydrate metabolism. The conclusion that may be drawn from these results is that the nerve fibres of the stalk are not of importance to anterior pituitary activity, since some animals display normal pituitary functions after stalk section, and the nerve fibres involved have no power of regeneration.

In an attempt to discover whether the portal blood-vessels of the stalk regenerate after section, and whether any regeneration could be correlated with the postoperative return of pituitary activity, the above experiments on stalk section in rats have been repeated. Harris (1949; and unpublished observations, 1949) found that regeneration of the hypophysial portal vessels and the return of oestrous cycles occurred in a high proportion of rats following pituitary stalk section. A second series, of 32 rats, in which small foreign bodies (usually paper plates) were placed between the cut ends of the stalk in an attempt to prevent such regeneration, was also studied. Fifteen of these latter animals remained anoestrous, and serial sections showed that in these cases the foreign body had been accurately placed and that no vascular regeneration had occurred. Of the other 17 animals in this group, 11 showed the return of irregular, and 6 the return of regular, oestrous cycles; histological examination showed a good correlation between the amount of regeneration of the portal vessels (allowed by misplacement of the foreign body) and the return of cycles.

The questions of what areas of the hypothalamus are concerned with the control of anterior pituitary secretion, and of how such control is mediated, are important; electrical stimulation of different regions of the hypothalamus and pituitary gland was applied in an effort to obtain relevant data. It is well known that under normal conditions ovulation in the rabbit involves coital excitation of a nervous reflex followed by anterior pituitary secretion and so follicular rupture. Using the remote control method (described in Section 1b above), it was shown (Harris, 1948c) that electrical stimulation of the tuber cinereum for 3 min. may be followed by a full ovulatory response, whereas similar stimuli applied directly to the pars distalis, pars intermedia or infundibular stem for periods up to 7½ hr. were not followed by ovulation. These experiments were performed in conscious rabbits so that different levels of anaesthesia could not be concerned with variations in response to stimulation. The theory of neurovascular transmission of stimuli accords well with the facts that stimulation of nerve fibres in the tuber cinereum of the hypothalamus excites anterior pituitary secretion of the gonadotrophic hormone, whereas stimulation of the nerve

fibres in the pituitary stalk (infundibular stem) or stimulation of the anterior pituitary itself does not result in secretion. If the anterior pituitary gland lacks secretomotor nerve fibres and is humorally excited via the portal vessels, it seems likely that the gland would be inexcitable to electrical stimulation.

c. Secretion of Adrenocorticotrophic Hormone

Since the mechanism of ovulation in the rabbit is rather exceptional among mammals, it appeared doubtful how far the above results could be applied to anterior pituitary secretion in general. That such application was valid appeared likely when it was found in a few rabbits that prolonged stimulation of the tuber cinereum resulted in a glycotropic response, that is, a marked decrease in sensitivity to the injection of small doses of insulin (Harris, unpublished observations, 1949). However, a more detailed study of the mechanism underlying the secretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland of the rabbit has been made. It is known that injection of ACTH in rabbits and other animals produces a temporary but marked fall in the absolute number of blood lymphocytes (Dougherty & White, 1943, 1944), and that emotional stress stimuli in mice and rats (Selye & Harlow, 1937) and in man (Pincus, 1947) produce a similar lymphopenia. It was found (Colfer, de Groot & Harris, unpublished observations, 1949) that emotional stress stimuli (restraint or subcutaneous faradism) constantly evoked a lymphopenic response in normal rabbits, but not in hypophysectomized animals, though injection of ACTH still produced a response after hypophysectomy. It was also shown that the adrenal medulla played no part in the lymphopenic response.

There was then available for investigation a reaction in the rabbit which could be indicated: emotional stress (neural excitation)→anterior pituitary gland→adrenal cortex→lymphopenia. To see whether the secretion of ACTH and a resultant lymphopenia could be evoked by hypothalamic stimulation, de Groot & Harris (unpublished observations, 1949) used the remote control method of stimulation with the primary coil enlarged to encircle the cage containing the rabbit. Thus the animal was in its usual surroundings and free to move, eat, groom the fur and so on during the period of stimulation and was not subject to concurrent emotional stress. It was found that the stimulation of the posterior region of the tuber cinereum and mamillary body resulted in a lymphopenia which was similar in time relations and magnitude to that following an emotional stress stimulus or injection of ACTH. Cervical sympathectomy did not abolish the response. Stimulation of other regions in the hypothalamus (including the supraoptico-hypophysial tract) and pituitary (pars and zona tuberalis, pars distalis, pars intermedia and infundibular stem) did not elicit the response. Some further observations were made (de Groot & Harris, unpublished observations, 1949) on the effect of various hypothalamic and pituitary lesions on the lymphopenia which normally follows an emotional stress stimulus. In two rabbits in which the zona tuberalis (the part of the anterior pituitary gland of the rabbit traversed by the portal vessels) was destroyed, and in some other animals in which the posterior part of the tuber cinereum or mamillary body was damaged, the lymphopenic response to stress was diminished or abolished. Thus, as in the case of the studies of gonadotrophic secretion, the theory of neurovascular transmission of stimuli is in accordance with the facts.

From the above, it appears that anterior pituitary secretion is influenced by nervous structures in the posterior wall of the tuber cinereum. Through this complex region passes the tubero-hypophysial tract and, although there is no direct evidence implicating this tract, it seems likely that it is concerned with the activity of the adenohypophysis.

It is of interest that from a different approach, Markee and his colleagues in America (Markee, Sawyer & Hollinshead, 1948; Sawyer, Markee & Townsend, 1949; Sawyer, Everett & Markee, 1949; Everett, Sawyer & Markee, 1949) have reached the conclusion that hypothalamic control of gonadotrophic secretion by the anterior pituitary gland of the rat and rabbit is humorally mediated by an adrenergic mechanism.

3. Conclusion

There can be little doubt that the majority of endocrine glands are under the control of the nervous system. The adrenal medulla and neurohypophysis are controlled by a rich, direct secretomotor innervation, whereas the adenohypophysis (and thus indirectly the thyroid, adrenal cortex and gonads) is probably brought under neural control by a local vascular link, the hypophysial portal blood-vessels. The hypothalamus forms an essential part of the neural mechanism influencing the endocrine series.

One of the striking facts emerging from recent work is the emphasis on emotional and psychological factors in the control of endocrine secretion. The relationship between emotional stimuli and the secretion of the adrenal medulla has long been known, but it is now apparent that the secretion of the antidiuretic, gonadotrophic and adrenocorticotrophic hormones from the pituitary gland may also be influenced by emotional states. It may be that the frontal cortex-hypothalamic relationship, which Fulton (1949) has recently emphasized in reference to the autonomic nervous system, is also of importance to the function of the endocrine glands. Eighteen years ago Le Gros Clark (1932) pointed out the importance of the fibre tracts uniting the cortex of the frontal lobe and the dorsomedial thalamic nucleus, and of the periventricular fibres which connect the dorsomedial thalamic nucleus and hypothalamus. Le Gros Clark suggested that this anatomical system links up a dualism of psychic life, the hypothalamus concerned with the internal environment (visceral activity and the pituitary gland) and the emotions, and the thalamus concerned more with stimuli arising in the external environment. The operation of frontal lobotomy has again focused attention on the fronto-thalamic connexions and it is of interest that there are many reports of cases, such as that of Hemphill (1944), in which lobotomy has resulted in a marked change in endocrine activity.

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THE AUTONOMIC SYSTEM OF MAN: DIGITAL VASOMOTOR RESPONSES

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1 Vascular changes associated with changes in respiratory rhythm
2 Responses to various stimuli
3 Blood-pressure changes in spinal man
4 Responses in opposite limb and in veins
5 Vasodilator function of the sympathetic nervous system
6 Conclusions
References

In man there are two main motor divisions of the nervous system. The first—the somatic efferent system—is concerned with the volitional control and reflex activity of skeletal muscle. The second—the autonomic nervous system—controls the activity of smooth muscle and glandular tissue. Anatomically the peripheral portions of these two systems are relatively distinct. The autonomic nervous system differs from the somatic in having an outflow to ganglia situated either along the side of the vertebral column or in close proximity to the tissues served by it. Like the somatic efferent system it has central connexions, which play a considerable part in governing its activities. The purpose of this communication is to discuss the recent work of several observers who have been concerned mainly with eliciting information regarding the nervous control over digital blood vessels and to place on record some further observations made in subjects with lesions of the spinal cord.

1. Vascular Changes Associated with Changes in Respiratory Rhythm

By the use of the finger plethysmograph, Goetz (1935) demonstrated that changes took place in the peripheral vascular bed following a deep breath. Using similar methods Bolton, Carmichael & Stürup (1936) made an especial study of the changes associated with alteration in the respiratory rhythm: they found that following a deep inspiration the volume of the finger decreased, and they noted that this response occurred nearly simultaneously in the digits of all four limbs; as this response was absent in the digits of a limb previously sympathectomized they considered that the response was mediated through activity of the peripheral sympathetic system and that therefore the response was in the nature of a vasoconstrictor reflex. Carrying their studies further, they concluded that the reflex was initiated by a stimulus associated with expansion of the chest wall during the inspiratory phase of the deep breath, and that the afferent stimuli were mediated by the intercostal nerves. Gilliatt (1948) re-investigated this reflex. In trained subjects he was unable to detect any appreciable difference between the response to thoracic inspiration and that to abdominal inspiration; he also found that the response was not connected with the fall in blood-pressure occurring during inspiration. He was thus unable to substantiate the assumption of Bolton *et al.* (1936) that the reflex was mediated by the intercostal nerves; at the same time he offered no information as to the probable site of the afferent nerve-endings responsible for this response. It would appear, however, that the afferent pathway for the response must reach the cord through the upper thoracic spinal nerves. Gilliatt, Guttmann & Whitteridge (1948) found in a series of patients with spinal injuries that, with lesions at the level of the lower cervical segments, deep inspiration caused constriction in the vessels of the fingers and often in the vessels of the toes; with lesions below the sixth thoracic segment no response in the toe occurred. Though there is considerable variability in the responses in the toes, the observations of these authors suggest that the entry for the afferent impulse is between the first and sixth thoracic roots.

2. Responses to Various Stimuli

Such responses, being constrictor in quality, were more readily observed when the digital vessels were in a state of dilatation. To obtain this state body-warming was essential, and the method used by Bolton *et al.* (1936) was that of immersion of indifferent limbs in water at 44–45° C. This method had been shown by Uprus, Gaylor & Carmichael (1936) as the most satisfactory for producing rapidly, and sustaining steadily, a state of vasodilatation of digital vessels. These authors demonstrated the difficulties in obtaining satisfactory vasodilatation of digital vessels by exposure to radiant heat and drew attention to the need for an adequate rise in blood temperature. It will be noted that, in a subject with a spinal lesion causing complete interruption of spinal pathways, vasodilatation of finger vessels could still be fully initiated by immersion of the insensitive legs in water at 44–45° C., but a greater rise of blood temperature was required than in healthy subjects. In subjects so warmed, Stürup *et al.* (1935) were able to obtain constrictor reflexes to a variety of stimuli—cutaneous and visceral pain, loud noise, cold, etc. In response to such stimuli the reflex occurred in all four limbs simultaneously. On occasions, without any known stimulus having been given, vasoconstriction could be noted as occurring, sometimes in the vessels of the toes alone and at other times in the vessels of the digits of all four limbs. These constrictions were examined by Doupe, Robertson & Carmichael (1937), who noted that they took place more frequently in the vessels of the toes and that when observed in the digits of all four limbs the degree of change was greater in the vessels of the lower limbs than in those of the upper limbs. As such spontaneous constrictions did not appear in the records obtained from the digits of a limb which had been previously sympathectomized, these authors believed that they were dependent upon the integrity of the sympathetic nervous system. They further observed that following a

variety of stimuli, such as cutaneous pain or sensation of cold induced by application of ice to an indifferent area of the body, digital vasoconstriction resulted, again more readily and to a greater extent in the vessels of the toes than of the fingers. This difference both in spontaneous and provoked responses was found to be absent in subjects with lesions of the cauda equina: the lesion had to be extensive enough to include the first sacral and lower lumbar roots, thereby producing sensory loss in the feet and calves. In such lesions, there was retention of the integrity of the peripheral sympathetic pathway, the outflow of which was above the level of the lesion: the vessels of the toes thus remained under active control of the sympathetic nervous system. In view of the absence of "spontaneous" vasoconstriction, combined with the greater response in the toe vessels in such patients, it was deduced that in the healthy subject the central nervous system was bombarded by afferent impulses from the leg area, which impulses tended to make it more easy to induce vasoconstriction in the vessels of the toes than elsewhere. Such a deduction might in part explain the observation of Lewis & Pickering (1931) and Pickering & Hess (1933) that vasodilatation was more easily obtained in the vessels of the fingers than of the toes. As far as is known to the present author, similar observations have not been made on animals. It may well be that, with the assumption of the erect posture, man has evolved an added means of controlling the blood supply, especially to the most dependent parts of the body.

As already noted, many forms of noxious stimuli, such as loud noise, flash of light, cutaneous pain, visceral pain and cold, produce vasoconstrictor responses. Carmichael *et al.* (1939) showed that distension of the duodenum also produced similar responses in the vessels of the fingers and toes; and not infrequently these responses followed a degree of distension which produced no conscious sensation. In later work (unpublished), these authors also found that similar results were obtainable in healthy subjects when the rectum was distended or the pressure within the bladder rapidly raised by injection of saline through a catheter.

3. Blood-Pressure Changes in Spinal Man

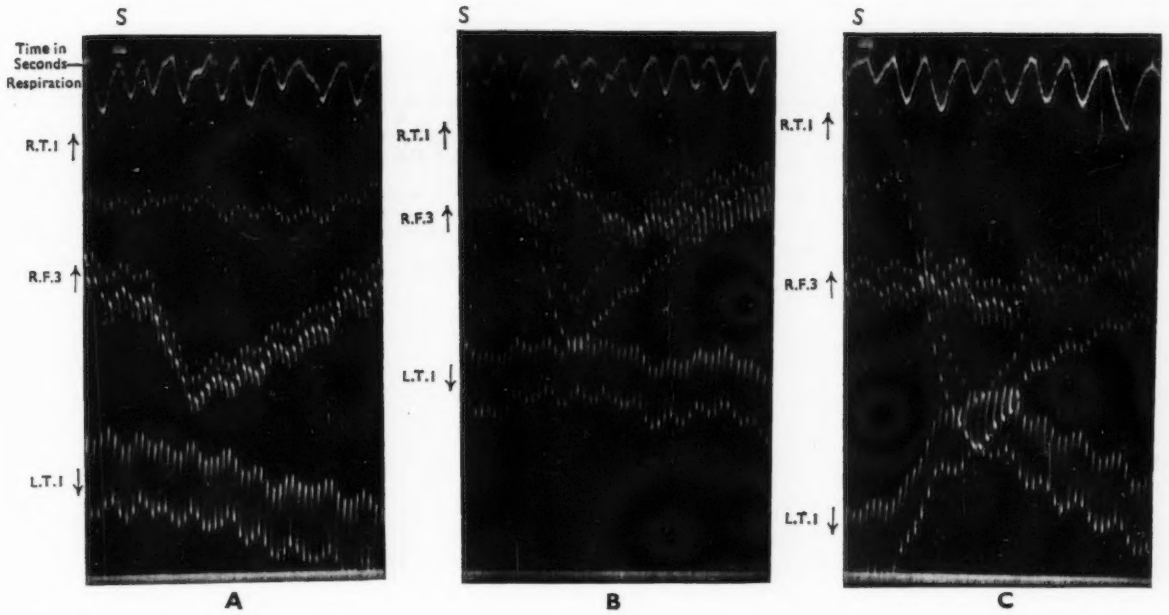
More recently, in patients with gun-shot wounds of the spinal cord, Guttmann & Whitteridge (1947) found marked changes in blood-pressure following distension of the bladder. As several of their subjects had lesions of the spinal cord at the level of the lower cervical segments, i.e. above the level of outflow of the sympathetic efferent fibres, the rise in blood-pressure resulted from activation of essentially spinal mechanisms. As they demonstrated a diminution in blood-flow in the fingers coincident with the rise in blood-pressure, it was taken that in spinal man digital vasoconstrictor reflexes could be elicited following a visceral stimulus.

In a series of patients suffering from traumatic or vascular lesions of the spinal cord it has been possible to examine in further detail the vasomotor reflexes. After having assured a steady state of vasodilatation of the digital vessels by immersion of one arm in water at 44–45° C., the responses of the vessels of the other hand and both feet were studied. In one subject, in whom as the result of a traumatic lesion of the spinal cord at the 8th thoracic segment there was an absence of sensation below that level, pin-prick or cold applied to the face or shoulders resulted in a ready vasoconstriction of the vessels of the fingers only. When a similar stimulus was applied to the lower abdomen or legs, vasoconstriction occurred only in the vessels of the toes; even when the stimulus was greatly increased, no response was observed in the vessels of the fingers. As already noted, vasomotor responses are more active in the toes than in the fingers in healthy subjects, irrespective of the site of the stimulus; hence the absence of vasoconstriction of the vessels of the toes in response to a stimulus applied to the upper half of the body may be taken as evidence that the descending pathways in the cord had been interrupted. Again, as even with severe stimuli to the lower half of the body nothing occurred in the finger vessels except, at most, a slight increase in volume probably due to the increase of blood-pressure, the ascending pathways in the spinal cord had also been interrupted. Thus vasoconstrictor responses in the toes were aroused by cutaneous stimuli when only spinal mechanisms were available. In another subject, again with a spinal lesion causing loss of voluntary control over movement of the legs and of sensation in the lower half of the trunk and legs, the application of a cold object to the front of one thigh resulted in a vasoconstrictor response limited to the vessels of the toe of the same side: if the area of stimulus was increased, then vasoconstriction appeared in the toes on both sides but never in those of the fingers (see fig. 1). In a third subject, with a vascular lesion at the level of the sixth thoracic segment, pin-prick above the level of the nipple resulted in vasoconstriction of the vessels of the fingers and no response in the vessels of the toes; when applied to the lower abdomen, pin-prick caused only a response in the vessels of the toes; however, when the stimulus was applied to a narrow zone above and below the upper level of maximum sensory loss in the trunk, vasoconstrictor responses occurred in the vessels of both the toes and fingers. This last observation is explicable on the assumption that, owing to the considerable overlap of sensory dermatomes on the trunk, the vasomotor centres in the cord, both above and below the level of the lesion, had received afferent impulses sufficient to initiate the mechanisms responsible for vasoconstriction in the digital vessels of both the upper and lower limbs.

4. Responses in Opposite Limb and in Veins

As in subjects with transverse lesions of the spinal cord it is possible to obtain responses in the vessels of the toes on the side stimulated, Elithorn and Crosskey have attempted to determine if in healthy subjects, following graded sensory stimuli, greater vasoconstrictor responses are obtainable in the limb stimulated than in the opposite limb. In a personal communication they have given information which shows that it is possible to obtain greater sudomotor responses in the arm stimulated. Using chiefly pain provoked by deep pressure, they noted that the skin resistance always altered more on the side stimulated. And as with vasoconstriction provoked reflexly by a painful stimulus a fall in skin resistance takes place at the same time, it is fair to deduce that, if the skin resistance alters more in the limb stimulated, the blood-vessels probably constrict more in that limb than in the opposite one. Absolute evidence of this, however, must await further investigation.

FIG. 1. PLETHYSMOGRAPH RECORD IN PARAPLEGIC SUBJECT



R.T.1 and L.T.1 refer to large toe of right and left foot respectively, R.F.3 refers to middle finger of right hand. Arrows point in direction of increase in volume. In A, at signal (S), pin-prick was applied to forehead, with resulting diminution in volume of finger only. In B, pin-prick was applied to right thigh, with diminution in right big toe volume only. In C, multiple pin-pricks to right thigh resulted in greater diminution in volume of right toe and also diminution in volume of left toe.

The observations recounted have been concerned with diminution in volume of a finger following a sensory stimulus. Wilkins, Doupe & Newman (1938) made a study of the changes in blood-flow associated with these changes and concluded that during the stage at which the finger diminished in volume there was a marked decrease in blood-flow to the fingers. Quite rightly then, these responses have been termed vasoconstrictor, and from the flow experiments it is apparent that the constriction at least takes place on the arterial side of the vascular tree. The literature contains few references to responses in veins to sensory stimuli. Doupe, Krynauw & Snodgrass (1938) demonstrated clearly that in an isolated segment of a subcutaneous wrist vein the tension within the segment increased following a cold stimulus applied to another part of the body, and they interpreted this as favouring nervous control of veins. Lewis & Landis (1930) also observed an increase in the size of veins following sympathectomy. It would thus appear that the veins are in part under the control of the sympathetic nervous system and probably respond in a manner similar to arterial vessels.

5. Vasodilator Function of the Sympathetic Nervous System

The possibility of the sympathetic nervous system having an active dilator function has also been the subject of study. Lewis & Pickering (1931) reported observations which, they suggested, supported the existence of vasodilator fibres to the vessels of the hands. The interpretation of their results, however, received criticism from Uprus *et al.* (1936). Discussing the response to warming of the body, Grant & Holling (1935) postulated at least two mechanisms: relatively gentle heating resulted in dilatation of the digital arterioles with resulting increased flow to the skin of the hands and feet—this response was believed to be due to release of vasoconstrictor influences and not due to active vasodilatation. If, however, the heating was more intense, causing generalized sweating over the trunk and limbs, there was an increase in temperature of the skin in the proximal portion of the limbs. From the experiments they carried out, they postulated that this increase in skin temperature was the result of active vasodilatation, the product of vasodilator nerves to the vessels of the skin. It is to be noted that their observations were concerned more with skin vessels in the upper arm than with the digital vessels.

6. Conclusions

There is adequate evidence to support the view that, in man, the peripheral sympathetic nervous system contains fibres whose function is to constrict the digital blood-vessels on the arterial side of the vascular bed. This constrictor function is initiated by both visceral and cutaneous sensations. The

reflexes are obtainable at spinal levels; with minimal cutaneous stimuli the reflex is an ipsilateral one, and with greater stimuli bilateral. There is less voluminous evidence that there are fibres whose function is to dilate digital blood-vessels; observations are available demonstrating the presence of vasodilating fibres to the skin vessels, especially in the proximal zones of the limbs. The veins are also under nervous control which is constrictor; the possibility of vasodilator fibres acting on veins has not been adequately investigated.

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BRITISH MEDICAL BULLETIN
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PART TWO · COMMENTARY
HISTORY · DOCUMENTATION

IN this issue of the Bulletin the books reviewed have been classified into a number of main sections which are listed below. It is hoped that this plan will facilitate reference to Part II by specialist readers, and that continuity of interest in the various fields of medicine will be maintained. There are, as before, sections devoted to annotations and news, historical notes, shorter notices, and a guide to the contents of current British medical periodicals.

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ANTIBIOTICS

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Antibiotics[1], by the Oxford workers to whom we owe the development of penicillin, has as sub-title "A survey of penicillin, streptomycin, and other antimicrobial substances from fungi, actinomycetes, bacteria, and plants". It is, however, more than a survey and could be described as "All about antibiotics" although, naturally, very recent developments have been too late for inclusion. In spite of this drawback, common to all books on growing subjects, *Antibiotics* surveys all aspects of this subject in sufficient detail to satisfy the requirements of all who want guidance in this branch of chemotherapy. That this is only a branch of chemotherapy can be gathered from the preface where it is stated:

> The term antibiotic, which is now in general currency, has been defined by Waksman as a substance produced by one micro-organism which is antagonistic to the growth of others. In this book plant products with antimicrobial properties have been included; these are often referred to in the literature as antibiotics, though strictly speaking it is doubtful whether the term should be applied to them. No consideration has been given to antibacterial substances of animal origin, such as lysozyme, nor to the complex phenomena associated with bacteriophage.

In some ways it is a pity that antibiotics should be arbitrarily separated from other antibacterial substances for, on the one hand, some antibiotics can be synthesized and even produced commercially, as has recently been done with chloromycetin, while on the other, as Florey and his colleagues mention here, their mechanism of action may be similar to that of well-known synthetic drugs. It is therefore quite likely that this distinction will disappear although the study of antibiotics as now defined will continue as a method of finding ready-made antibacterial substances which may turn out, like penicillin, to be useful chemotherapeutic drugs as they are, or may, after the determination of their chemical structure, give a lead to new valuable substances. In any case it is as well that this book is confined to substances produced by living organisms, because it already comprises 1774 pages in these first two volumes, which deal with all aspects except clinical application.

From the general historical introduction it becomes apparent that the bacteriological techniques now in current use for the detection of antibiotics had all been thoroughly exploited many years ago. Most of this work, however, was abortive in that there was little co-operation between the biological worker and the chemist and indeed it is doubtful whether such co-operative work would have been fruitful because many of the biochemical procedures, which are so essential for the separation and purification of antibiotics, were not then sufficiently developed. In this sense it may be said that the early work on antibiotics was ahead of its time in much the same way as the early experiments which eventually led to the isolation of insulin were frustrated because the methods of blood analysis had not then been sufficiently developed to control their application to man.

That the chemist plays a major role in the hunt for new antibiotics is evident from this book. Taking penicillin alone we find that it requires 13 chapters, comprising 284 pages, to outline its chemical aspects. But though the biologist owes much to the chemist for his help in developing these antibiotics, the chemist too is amply repaid by being introduced to chemical structures that have never before been encountered in nature. Thus the linking of these sciences is paying dividends on both sides—on the one hand increasing the number of new antibacterial substances, of which two, chloromycetin and aureomycin, have recently proved their worth in infections which have been unresponsive to other remedies, and on the other the widening of the range of the chemist's experience.

After the introduction the first volume describes the methods used for the detection and development of antibiotics, and gives details of a large number of these substances from fungi, actinomycetes and plants. The most satisfactory method of detecting antibiotics is the most familiar, namely, sowing the organism to be tested for antibiotic properties on a nutrient agar plate which is also sown with the micro-organism against which antibiotic action is sought. Florey and his colleagues find this a more suitable method than tests made in fluid media. The micro-organisms against which action has been sought have generally been *Staph. pyogenes* and *Bact. coli*, being representative of the gram-positive and gram-negative bacteria, the former of which are usually more sensitive to antibacterial substances. This has been a most useful procedure for screening micro-organisms for antibiotic activity and can also be used for testing extracts of larger organisms such as plants, in which case the extract is placed in a cylinder or in a hole in the agar, so allowing any active substance to diffuse into the medium. With this now classical technique, on the basis of which Sir Alexander Fleming discovered penicillin, much time has been saved in the rapid detection of possibly useful antibacterial substances, active not only against *Staph. pyogenes* and *Bact. coli* but against other micro-organisms. Of these there have now been described at least 80 well-defined antibiotics and many hundreds of active principles. There still, however, remains the possibility that valuable chemotherapeutic substances may be missed by this method, as for example substances like the sulphonamides which, being antagonized by some metabolite present in ordinary media, would not show any effect by cultural methods, but by an interference with some aspect of bacterial metabolism to which animal tissues are indifferent might prove to be of great therapeutic value.

The second volume, which comprises 1144 pages including appendix (65 pages), bibliography (84 pages), indexes (112 pages) to vols. I and II, deals with penicillin and streptomycin and has two final chapters, one on the action of antibiotics on bacteria and another giving conclusions. In the historical introduction to penicillin, Sir Alexander Fleming's discovery of penicillin is fully described and then there is a full account of the early work at Oxford which, owing to the Second World War, was greatly hampered by many difficulties, particularly as regards supplies of essential equipment.

[1] For particulars, see p. 394.

Though little is said here it is obvious that this must have been a heart-breaking time for Florey and his colleagues, who knew that they had a preparation which would revolutionize the treatment of infections, particularly in war wounds, and were not able to get on fast enough because of war-time restrictions. The later development of penicillin and its dramatic effect in clinical practice both in the battlefields and in the civilian population are now so well known and recognized that there is no need to say more here. It is, however, noticeable that the Oxford team do not claim for penicillin all the credit for the dramatic improvements in the surgical treatment of war wounds; they say:

> Much of the success attending the use of penicillin for the treatment of the wounded is to be attributed to the increasingly high quality of war surgery, and this again received a great stimulus because surgeons armed with penicillin could, if their technique were sufficiently good, suture even the most severe wounds without the danger of spreading sepsis, and with great benefit to the patient.

In the light of their intense research on antibiotics and their application, the Oxford workers have formulated the properties desirable in a chemotherapeutic agent for systemic use. The agent should have little toxicity to the animal body in comparison with its toxicity to sensitive micro-organisms. It should be active in low concentrations for otherwise the doses would be impracticably high. It should be active in the presence of normal and pathological body fluids and should not be inactivated by tissue enzymes. It should not be antigenic because of the great danger of producing allergic phenomena. For most purposes it should be significantly soluble at the pH of body fluids. A great advantage in an antibiotic would be stability sufficient to allow of its administration by mouth.

So far penicillin, with the one single disadvantage of not being usefully administrable by mouth, is the exceptional antibiotic that fulfils these criteria, but recently chloromycetin and aureomycin, two antibiotics that can be given by mouth, have shown exceptional activity against a number of infections. How these new substances will compare with penicillin in clinical practice has yet to be seen. There is, however, no doubt that penicillin has come to stay and will be our main weapon in combating infections when properly used. The other antibiotics will have their place in supplementing penicillin in the treatment of infections in which penicillin is less applicable.

This book will be essential to all those who are interested in chemotherapy and should have a place in every hospital library and medical laboratory. All other works of a similar nature in this field fall far short of this reference book; and it is more than an exhaustive review because of the high standing of the authors who, beside their work on penicillin, have themselves isolated and studied many new antibiotic substances. Their critical evaluation of the subject will therefore command universal respect, and indeed we owe these busy workers a tremendous debt of gratitude for sparing their time to give us the benefit of their unique experience.

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Annotations & News

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MEDICAL CONGRESSES 1950

Autonomic Nervous System. The Austrian Medical Conference will be held in Salzburg from 7–9 September, 1950. The main subject of the Conference will be "The Autonomic Nervous System and its Influence upon the Course of Illness". Enquiries should be sent to the Sekretariat der Van Swietengesellschaft, Landeskrankenhaus, Salzburg.

Cancer. The Fifth International Congress on Cancer will be held in Paris at the Sorbonne, from 15–22 July, 1950. The Congress will coincide with the 50th anniversary of the discovery of radium by Pierre and Marie Curie, to the celebration of which members of the Congress are invited. Papers to be read will deal with the following branches of the subject: biology and experiment, pathology, clinical approach, therapy, social implications of the fight against cancer. Full details may be obtained from l'Union Internationale contre le Cancer, 6 Avenue Marceau, Paris VIII.

Comparative Fertility. The new Society for the Study of Comparative Fertility will hold its inaugural meeting at a conference to be held at the premises of the Zoological Society of London on 16–17 June, 1950. Further particulars may be obtained from Dr G. I. M. Swyer, Obstetric Hospital, University College Hospital, London, W.C.1.

Diseases of the Chest. The First International Congress on Diseases of the Chest will be held in Rome from 17–20 September, 1950. The Congress is to be held under the auspices of the council on international affairs of the American College of Chest Physicians and the Carlo Forlanini Institute. Further information may be obtained from Professor A. Omodei Zorini, Carlo Forlanini Institute, Rome, or from Dr Chevalier L. Jackson, 500 North Dearborn Street, Chicago 10, Illinois, USA.

Haematology. The International Society of Haematology will hold a Congress from 21–26 August, 1950, in Cambridge. The provisional programme includes the following subjects: (i) Therapy of Anaemias; (ii) Hyperpleurism; (iii) Leukaemia, Including Therapy of Leukaemia; (iv) Physiology and Pathology of Coagulation and (v) Immunohaematology. Further information may be obtained from Dr Martin Hynes, Department of Medicine, University of Cambridge.

History of Medicine. The Sixteenth Congress of l'Union Internationale d'Histoire de la Médecine will form part of the Sixth International Congress on the History of Science. This will be held in Amsterdam from 14–20 August, 1950. Further information may be obtained from Professor Ir R. J. Forbes, Haringvlietstraat 1, Amsterdam-Z, the Netherlands.

Maternity and Child Welfare. The Annual Conference of the National Association for Maternity and Child Welfare will be held in London from 28–30 June, 1950. The theme of the Conference will be "The Child and its Environment" and introductory papers by experts in the field will be followed by group discussions. Further information may be obtained from the Honorary Secretary, National Association for Maternity and Child Welfare, 5 Tavistock Place, London, W.C.1.

Medical Photography. An International Exhibition of Medical Photography will be held in London from 12–24 June, 1950, by the Medical Group of the Royal Photographic Society. It is hoped that medical photographers from all parts of the world will submit their work for selection. Entry forms may be obtained from the Honorary Secretary, Kenneth G. Moreman, 16 Princes Gate, London, S.W.7.

Psychiatry. The International Congress of Psychiatry will be held in Paris from 18–27 September, 1950, and will include an exhibition of psychopathological art. The secretary-general of the Congress is Dr Henri Ey, 1 Rue Cabanis, Paris XIV.

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GALEN AND RHAZES: A SPANISH TRANSLATION

The last twenty years have seen the growth of a widespread interest in the history of medicine in most of the countries of Latin America. It is by no means the interest of the dilettante, but a genuine scholarly discipline fostered and maintained by numerous university chairs in the subject and a number of flourishing specialist institutes. The Institute of the History of Medicine of the University of Buenos Aires has long been known for its journal, the *Publicaciones*, which is distributed throughout the world. Formerly edited by Professor Juan Ramon Beltran, it is now under the able direction of his successor in the chair, Professor Aníbal Ruiz Moreno. Volume 12,[1] for the year 1948, was published a few months ago and has recently arrived in this country.

The first part of this volume is a most important contribution to Galenic literature, for it is devoted entirely to a Spanish translation of two of Galen's treatises on the pulse. Working in collaboration with the distinguished Spanish philologist Dr Antonio Tovar, Professor Moreno has based his version on Kühn's edition which, if not perfect from a philological standpoint, is the best available, since Galen's writings on the pulse have not yet found their way into the modern critical edition of his works which began in the *Corpus medicorum graecorum* in 1914. There is no complete translation of Galen's works into any modern language, and Professor Singer's appeal for a complete English translation has not shown any obvious results, although I believe that such an undertaking has been started in the United States of America.

Galen wrote seven distinct treatises on the pulse, viz., (i) *De usu pulsuum*; (ii) *De pulsibus ad tirones*; (iii) *De pulsuum differentiis libri IV*; (iv) *De dignoscendibus pulsibus libri IV*; (v) *De causis pulsuum libri IV*; (vi) *De praesagitione pulsibus libri IV*; (vii) *Synopsis librorum suorum de pulsibus*. These were published in their entirety in the *Opera de pulsibus* in 1532, but the only modern work on any of them is Johann Gossen's critical discussion of the *Synopsis* (Berlin, 1907).

It is clear then that Professor Moreno, in undertaking the translation into Spanish of all seven treatises, has found a neglected corner in the field of Galenic studies, and one which is most important for the influence and strength of the Galenic tradition, so that his work will be of value to scholars not only in the Spanish-speaking countries but throughout the world.

He has wisely chosen to begin the series with (ii), the compendium on the pulse for students, a short tract of only twelve chapters, and to proceed to (iii) the four books on the differences of pulses. The chapter headings throughout are taken from the sixth Giunta edition (Venice, 1586); footnotes are sparse, but there is an excellent index of subjects, an index of authors cited in the text, and another of references to Galen's other works. A most useful feature is the glossary of technical terms used by Galen, with their modern Spanish equivalents.

To judge the translation itself one would need to be expert not only in Greek and Spanish philology but also in Galenic physiology and medicine; for those who do not possess this rare combination of attainments the authority and reputation of the two translators is sufficient recommendation.

The second part of the volume under discussion is also devoted almost entirely to the Spanish translation of a classic text, the book on smallpox and measles by Rhazes. The indefatigable Professor Moreno is entirely responsible for this version. As he confesses in his preface, there is no Spanish orientalist with sufficient knowledge of medicine to undertake a direct translation from the Arabic text, and he decided to make a Spanish version of the English translation by W. A. Greenhill which was published by the Sydenham Society in 1848. He could not have made a better choice, and it must be of particular pleasure to English historians of medicine to find the work of one of their greatest predecessors reappearing in this guise more than a century after it was written.

Rhazes' work on the smallpox and measles is too well known to warrant any detailed account here. It is of course the first classic account of both diseases, and for nearly a thousand years there have been few writers on the subject who have not been indebted to it or referred to it in some way or other. The present text is preceded by a useful introduction on the author's life and work.

[1] For particulars, see p. 394.

Concluding the volume is an interesting account of the organization of military hygiene in the Brazilian war of 1827. Written by Professor Moreno in collaboration with Vicente A. Risolía and Rómulo D'Onofrio, this paper was read at the seventh National Medical Congress.

After perusing this very impressive volume I cannot resist the temptation to revive the perennial complaint of the singular lack of a scholarly British journal devoted to the history of medicine. With some of the finest medical libraries in the world and a wealth of material for study, we are still without one; nor is there in any of our universities an institute or even a chair in medical history. The superiority of North America in this respect is already acknowledged. The astonishing activity in South America since 1939, of which this volume is one further proof, should do something to stimulate the responsible authorities in Great Britain.

F. N. L. Poynter

1542

JOURNALS NEWLY RECEIVED

The *Bulletin of the Hong Kong Chinese Medical Association* entered its second year of publication with the first number to reach us (vol. 2, no. 1, April 1949). The Editorial Board at that time felt assured of its continuance " . . . as a medium of communication and information for the medical fraternity in Hong Kong as well as a means of union among the members of our Association," and invited contributions, which should be addressed to the Editor-in-Chief, Dr H. C. Chan, Bank of Canton Building, 4th Floor, Hong Kong. The editorial discusses the question of administration of intravenous injections by nurses, which had been raised in the correspondence columns of the previous number, and requests the co-operation of the Association's members in the current anti-tuberculosis campaign. Original articles and case reports are published, and a few abstracts. The Association's annual report is incorporated in the *Bulletin*, and refers to the " very good medical films " which had been shown to the Association by the British Council during the period under review.

* * *

Archivos Argentinos de Reumatología (Buenos Aires) has published as part of vol. 11, 1949, a special number on the histopathology and pathogenesis of acute rheumatic disease (Bouillaud's disease). The number consists of a monograph by Dr Pedro I. Elizalde, professor of pathological anatomy and physiology in the National University, Buenos Aires. Typical rheumatic lesions of the cardiovascular system, lungs, liver, kidneys, thyroids and thymus, muscular system, tendons and skin are described, each section being illustrated with photomicrographs. The author comments on the high incidence of tonsillar infection and concludes that this is the most frequent cause of acute rheumatic disease.

Vol. 12, no. 2, of the same journal contains two articles on rheumatic disease and allergy, one on climate and rheumatism and a summary of the proceedings of the Seventh International Congress on Rheumatism which took place in New York in May–June 1949.

We have recently received vol. 14, no. 1, 1949, of the *Revista de Instituto Bacteriológico Malbrán* (Buenos Aires). This number consists of 33 reports of original work by members of the institute's staff. Subjects to which groups of four or more studies are devoted are influenza virus " A ", *Coccidioides immitis* Rixford et Gilchrist, and *Leptospira*. The number is illustrated with drawings and with nearly 50 photomicrographs of a good standard.

* * *

From the Department of Parasitology, University of Chile, we have received two numbers, vol. 4, no. 1 and no. 2, 1949, of the *Boletín de Informaciones Parasitarias Chilenas*. Each number contains three original short articles, an abstract of an important paper on a relevant subject, and a section of news.

The Department of Parasitology and the School of Medicine of the University of Chile have been completely destroyed by fire, and the head of the Department, Professor Amador Neghme, appeals for assistance in re-equipping the laboratories. Publications concerning amoebiasis, trichinosis, trypanosomiasis, yellow fever and hydatid disease are urgently required, and papers dealing with parasitology, biology, epidemiology, and public health in general, would be appreciated.

The introduction during the summer of 1949 of a limited scheme of BCG vaccination in Great Britain lends interest to a recent special number of the *Boletín Médico Social* (Santiago de Chile), organ of the Caja de Seguro Obligatorio (department of compulsory national insurance). In a covering letter, Dr Alfredo Biondi E., director of medical services in that department, refers to the slow economic development of Chile and its depressing effect on the general standard of living, and notes that " The mortality rate of tuberculosis does not seem to have decreased in the last fifty years (240 per 100,000 inhabitants)."

To break into this discouraging situation the Caja de Seguro Obligatorio launched a national propaganda campaign in favour of BCG vaccination. The campaign had the support of the medical profession, voluntary bodies and other government departments, and was followed by practical measures which it is hoped soon to co-ordinate into a national scheme. No. 164–168 of the *Boletín Médico Social*, May–September 1948, is issued in association with the campaign. Besides three articles by Chilean workers discussing national and local aspects of BCG vaccination, it contains ten others selected and translated from European and American literature; among these are two by Dr Arvid Wallgren, the Swedish pioneer in this field, and one by Dr C. Guérin. A third section includes a detailed history of BCG vaccination in Chile from 1925 to 1948, a group of official documents relating to the campaign, and correspondence on the subject taken from the *British Medical Journal*. The number is illustrated, and English summaries are appended to many of the main articles.

* * *

Minerva Chirurgica (Turin), another member of the famous group, published fortnightly, is now in its fourth year. Vol. 4, no. 17, September 1949, contains articles on conditions associated with the right half of the abdomen (Professor G. Peracchia), pharyngo-oesophageal diverticula (P. L. Bruzzone), treatment of secondary haemorrhages (Dr M. Pittoni), a case of intestinal occlusion from ascaridiasis (Dr M. Romano), and Breitman's test for autonomic nervous function in postoperative and post-traumatic states (C. Scartozzi & G. Martinetto). A section of abstracts from current literature completes the issue.

The group of medical journals published by Edizioni Minerva Medica is further enlarged by the appearance of *Minerva Ginecologica* (Turin), vol. 1, no. 1, October 1949. This journal succeeds *Folia Gynaecologica* and *La Ginecologia*, the history of which is outlined in the introduction. Original articles include two on pneumo-amniography (Drs G. Vecchietti and E. Robecchi), one on surgical treatment of retroflexion of the uterus by the Acconci method (Dr M. Repetti), and one on sympathectomy in painful pelvic syndromes (Dr G. Passera). There is also a section of abstracts from literature, a guide to journals of obstetrics and gynaecology, notes and news, and a section of " Varia " touching on medical aspects of history and art. Summaries in French, English and German of the original articles are grouped together at the end of the journal.

* * *

We have received two further volumes in the series *Colección Española de Monografías Médicas*, published by Ediciones BYP of Barcelona, under the direction of Dr J. Puig Sureda. Each of these volumes is a double number: the first (1949, no. 99–100), *Bronquitis crónicas*, is by Dr D. Antonio Marcos Barbero; the second (1949, no. 101–102), *Osteoperiostitis*, is by Dr D. V. Bosch Olives. As is usual in this series, each volume includes, in addition to the main monograph, a section of short original articles on a number of subjects under the heading: " Practical notes on diagnosis and treatment."

* * *

The Sociedad de Medicina del Deporte y del Trabajo and kindred organizations in Argentina celebrated the first national congress of industrial medicine in Buenos Aires in May 1948. Its proceedings were published in two volumes, separately paged, during 1949. More than 50 contributions are included, representing nutrition, physiology, legislation, vocational guidance, accident prevention, industrial diseases and toxicology, history of industrial medicine,

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Historical Notes

1543

THE ROYAL COLLEGE OF SURGEONS OF ENGLAND 1800–1950

A century and a half is not a long history for an English institution. Yet, though the Royal College of Surgeons of England, younger than its sister colleges in Edinburgh and Dublin, is this year celebrating only the third jubilee of its charter of incorporation, it is the direct successor of guilds and companies of London surgeons whose lineal ancestry may be traced back without a gap for more than five hundred years.

Towards the end of the eighteenth century the Company of Surgeons was neglecting its business. It had separated from the Barber-Surgeons, with high hopes for independent success, in 1745. But after half-a-century it became legally necessary to make a fresh start. The reformers decided to begin on new lines and, instead of renewing the Company, founded under Royal Charter the College which is now looking back over 150 years of good work. And now the College has re-equipped itself in the most recent years to play an ever more active and useful part in the medical world of the future.

The new College of 1800 inherited from its predecessor a house, 41 Lincoln's Inn Fields, to which the Company had intended to move from its Hall in the Old Bailey its records and such plate and pictures as had been collected since 1745, and, above all, John Hunter's museum, the charge of which had been entrusted to the Company by Parliament. Hunter, the greatest biologist and surgeon of his day, had died in 1793, but the museum was still in his executors' hands. The College also inherited the duties of arranging anatomy lectures, and of examining candidates for the practice of surgery in London and in the national armed Forces. Of these duties the old Company had neglected all but the examining. The new College has developed them immeasurably and undertaken many other important activities. Since the reform of 1843 it has held a truly national position as the Royal College of Surgeons of England, not merely of London as theretofore. Its Fellowship examination instituted at that time is generally recognized as the most honourable surgical examination in Great Britain, if not in the world, and has long attracted aspirants from the distant dominions.

Between 1800 and 1843 the College was very much alive. It had built itself a fine house and museum in 1813, and rebuilt on a more ample scale in 1835 the familiar building, later much extended, but badly damaged in 1941, which is soon to be restored in yet more splendid scope. The Museum had been displayed and developed, and a fine library rapidly collected, both under highly competent officers. But the constitution remained antiquated: all control was in the hands of a self-perpetuating Council, whose members were elected for life from the then small circle of the metropolitan hospital staffs. The good work done by the College could not silence the objectors in the 1830s, when reform was on every man's lips. Fortunately wise opinions prevailed within the Council, and at the instigation of G. J. Guthrie and others, with Benjamin Brodie as the active spirit, a new Charter was obtained in 1843, which established the Fellowship on the basis of an advanced examination in the surgical sciences. It made the Council elective, reasonably curtailed its privilege and tenure, and as said above made the College a national instead of a local body. So far-sighted was Brodie that no fundamental change in the constitution has been found necessary. Supplementary charters have enabled the College to improve its methods and extend its field of work. A Licence in Dental Surgery was instituted in 1859. In 1883 it joined with the Royal College of Physicians in forming the Conjoint Examining Board to manage the qualifying examination (M.R.C.S., L.R.C.P.); and a number of special diplomas were soon introduced. Women were admitted to full equality within the College in 1926. Since the end of the war in 1945, Faculties of Dental Surgery and of Anaesthetists have been formed. By these reforms the College has grown a hundredfold in membership, and the members are being drawn more than ever into touch with active collegiate life.

Every national institution has a double history. It plays its part, through the distinguished men who give their counsel to its deliberations, in the affairs of the nation. It also has its domestic history in the work of its officials and scientific staff. The College of Surgeons has thus taken a prominent part throughout its history in promoting the education and maintaining the professional standards of surgeons, and in wider medical questions. But of the great surgeons who have filled the presidential chair only a few, such as Brodie or Moynihan or Lord Webb-Johnson, have left a lasting mark on its domestic history. The greatest member of the College Council, Lister, was never President, just as a century earlier John Hunter served on the Court of the old Company but never became Master of it.

The Hunterian Museum was designed by its founder to exhibit on a very extended scale a comparative survey of biological form and function. Hunter seems to have been the first man to conceive of surgery as the application of a knowledge of all living processes to the cure of disease. By the work of Richard Owen, conservator of the museum from 1842 to 1856 and assistant to William Clift for the previous fifteen years, Hunter's collections were reorganized and extended, and fully explained in a series of detailed and illustrated catalogues, which were constructive contributions to the advancing knowledge of physiology and pathology.

One of the conditions under which Parliament entrusted the Hunterian Museum to the care of the College was that Hunterian Lectures should be regularly delivered. Competition to deliver one or more of these lectures, on a topic submitted by the lecturer, has always been keen among rising surgeons of a scientific bent. They have been supplemented by continuous lecture courses and demonstrations of museum specimens given every year by the members of the College's scientific staff. Among these regular courses are the Arris and Gale lectures, delivered under endowments dating back to 1645 and 1507. Since 1946 the College has established an integrated system of postgraduate teaching, and has opened a Residential College in two houses adjoining the central College building. This is only a forerunner of the Nuffield College of Surgical Sciences which will before long rise from the bombed site at the other side of the College. The late war, which did irreparable damage to the Hunterian Museum in the disastrous air-raid of May 1941, provided opportunity for resurgence on an unprecedented scale, which has been seized and exploited by Lord Webb-Johnson, President 1941–49, with masterful foresight. The College has been fortunate in attracting princely endowments for its scientific work, as well as countless donations large and small towards the rebuilding fund, and gifts of specimens for the re-equipment of the museum, not only at home but from overseas.

ANNOTATIONS AND NEWS

Continued from page 359

psychology, hygiene and welfare, absenteeism, women in industry, and evaluation of work. The report is well printed, and illustrated where appropriate.

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The following journals have also been received:

Acta Societatis Medicorum Upsaliensis (Stockholm), vol. 55, nos. 1 & 2, 1950

Aparato Respiratorio y Tuberculosis (La Paz, Bolivia), year 6, nos. 21–22, 23, 1949

The Diabetic Journal (London), vol. 5, no. 12, 1949

Gaceta Médica de Lima (Lima), vol. 4, no. 3, 1949

Les Instantanés Médicaux (Paris), nos. 1 & 2, 1949 & 1950

Liječnički Vjesnik (*The Journal of the Medical Association of Croatia*) (Zagreb), vol. 71, no. 3, 1949

Revista de la Federación Médica de Guatemala (Guatemala), year 3, nos. 14 & 15, 1949

Szovjet Orvostudományi Beszámoló (Budapest), vol. 1, no. 1, 1949

Two or three extended periods of great productivity stand out in the College's history in the past 150 years. In the first of these, besides Owen's work in the museum, mentioned already, rapid progress was made in the 1830s in collecting a library which should be a working tool for the College's staff and students, and a real academic storehouse of the records of surgical discovery through the ages. Fifty years later, at the time when periodical publications were beginning to proliferate, the library was thoroughly reorganized. When the College celebrated its centenary in 1900 it possessed one of the finest medical libraries in the country. In the succeeding decades it was outstripped by other libraries of wider scope. But by virtue of its rich resources, early laid down, in surgical classics and basic scientific periodicals it remains one of the premier centres of medical literature in the Commonwealth, and fills an important niche as the specialist library of anatomy and surgery among the many medical libraries which have grown up during the twentieth century. The Council has always encouraged its use by those scientists and students beyond the immediate circle of the College who can produce suitable evidence of their bona fides.

Scientific research has not been neglected. The range of Owen's work in comparative anatomy, in which he included the palaeontological evidence, is still unrivalled. Sir Arthur Keith's epoch-marking work in evolutional anthropology showed what value the insight of genius could derive from the Museum's vast osteological collections, which to others seemed a Golgotha. In more recent years the Buckston Browne Farm and the Bernhard Baron Laboratories, both managed by the College, have contributed to the elucidation of urgent surgical problems: the pioneer work on surgery of the heart by Laurence O'Shaughnessy, a victim of the war, may be quoted. For nearly fifty years the College has been jointly responsible with the Royal College of Physicians for the Imperial Cancer Research Fund, from whose laboratories a series of fundamental *Scientific Reports* has issued. The College itself publishes an *Annual Scientific Report*, and has from time to time issued many publications of scientific value, mostly in connexion with the Museum. Twenty years ago the record of past Fellows was published in *Plarr's lives of the Fellows*, 1843–1930, the work of a former librarian, Victor Plarr. Three years ago the monthly *Annals* of the College were inaugurated, and have already achieved popularity. This journal publishes the scientific lectures delivered at the College, as well as recording current activities and describing historic possessions. By domestic activity no less than by the leading part it plays in the surgical life of the Commonwealth, the College continues to promote, in the words of its Latin motto, " Arts useful to all."

W. R. Le Fanu

1544

THE DIFFERENTIATION OF FUNCTION OF THE ANTERIOR AND POSTERIOR ROOTS

Historical Background

When Robert Whytt (1714–1766) became Professor of the Theory and Practice of Medicine at Edinburgh, his old university, in 1747, he busied himself chiefly with physiological experiments, in the course of which he was the first worker to localize a reflex. He obtained lasting dilatation of the pupil by compression of the optic thalamus. Whytt also showed, by experiments on a frog, that an intact portion of the spinal cord suffices for a reflex.[1] Whytt gained prominence in Germany, Switzerland, and France because his theories on neurophysiology brought him into conflict with Albrecht von Haller (1708–1777) of Berne.[2] Fearing, in his history of reflex action, says of Whytt:

> Though Descartes is frequently credited with being the originator of the doctrine of reflex action, this is based largely on his chance use of an analogy in support of his theory of the human body as a material machine directed by a rational soul . . . In contrast, Whytt, under involuntary motion, as a result of a penetrating psychological and physiological analysis, recognized a separate class of animal action.[3]

On the clinical side, Whytt is noted as the first to describe tuberculous meningitis.

Another Edinburgh professor, Alexander Monro *secundus* (1733–1817), who described the foramen in the brain, which bears his name, pointed out that the ganglia of the spinal nerves are formed on the posterior roots and that the anterior roots possess no ganglia:

> Instead of this, I have observed, that the posterior fasciculus only of the spinal nerve enters into the ganglion; and that authors have been deceived, by not having slit open the external coat of these nerves.[4]

But as yet there was no appreciation of the true function of the anatomical arrangement.

The first person to insist on the separate functions of the anterior and posterior roots was Alexander Walker (1779–1832),[5] a lecturer in anatomy at the extramural school.[2] He was a brilliant man, though an eccentric; an excellent linguist, his translation of the reports of foreign workers on his own subject (*Documents and dates of modern discoveries in the nervous system*, London, 1839) is unimpeachable.[5] Walker was naturally deeply perturbed when no-one of his time gave him credit for his speculations. He apparently based his inferences on purely anatomical evidence, however, and unfortunately he made one mistake—he thought the anterior root was sensory and the posterior one motor.

Charles Bell (1774–1842) was the first person to discover that the anterior roots were motor in function. He was the youngest son of an Episcopalian clergyman in Scotland and was devoted to his mother: " . . . for twenty years of my life," he wrote on one occasion, " I had but one wish—to gratify my mother and do something to alleviate what I saw her suffer." After studying medicine in Edinburgh, he took over his brother John's class in anatomy there, but in 1804, to avoid being caught up in the vendetta being waged against his brother by the Professor of Medicine, James Gregory, Charles Bell went to London to seek his fortune. It was, however, in the extramural school at Edinburgh that Bell's attention was first directed to the study of nerves.[6]

Charles Bell had a long way to go before he was knighted for his physiological discoveries, but already he had been not unsuccessful. As a student in Edinburgh he published *A system of dissections*, in two volumes (Mundell, Edinburgh, 1798–1803), illustrated by his own drawings. (It must have been very inconvenient to use on the dissecting table, because it is so large; but then perhaps the idea was to ensure that the student read the relevant section before starting work.) His *Essay on the anatomy and philosophy of expression* (London, 1806) was in after years so to captivate Queen Victoria's interest that she read it with rapt attention for two hours; whilst the Nabob of Arcot had a copy bound in red morocco and satin.

Bell, however, was determined to make a discovery as fundamental as Harvey's on the circulation of the blood. As early as 1807 Bell began to formulate the conceptions which were to bring him fame; and in 1810 he wrote to his brother George:

> Next it occurred to me that all the spinal nerves had within the sheath of the spinal marrow two roots—one from the back part, another from before . .
> Experiment 1. I opened the spine and pricked and injured the *posterior* filaments of the nerves—no motion of the muscles followed. I then touched the *anterior* division—immediately the parts were convulsed.
> Experiment 2. I now destroyed the posterior part of the *spinal* marrow by the point of a needle—no convulsive movement followed. I injured the anterior part, and the animal was convulsed.[7]

When Bell married in 1811 the young bride soon found that research on nerve function " was the important object of his life ", and she tried to understand what he talked about. In this year Bell printed privately his *Idea of a new anatomy of the brain*; *submitted for the observations of his friends* (Strahan & Preston, London, 1811). Here he referred to the results obtained in the experiments described in the year before in his letter to his brother. This pamphlet has been reproduced in full in *Medical Classics* (1936, **1**, 105) and fairly fully in J. F. Fulton's *Selected readings in the history of physiology*.[5] The copy in the Library of the Royal College of Surgeons of England has a list of the persons to whom Bell sent his essay, copied from a list in Bell's own handwriting. This shows that he presented copies to John Abernethy, Matthew Baillie, Sir Astley Cooper, Dr. Burrowe of Philadelphia, and others. A transcript of a letter from the printers, also annexed to this copy, establishes that Bell had 100 copies printed at the end of August 1811. It is clear from the *Idea* that at this time Bell still adhered to the old doctrine of the " sensibility " and " insensibility " of nerves.

Since 1822, when Magendie first put forward his claim, there has been controversy as to whether he or Bell deserve credit for the discovery of the functions of the anterior and posterior roots. Béclard, a fellow countryman of Magendie, openly declared in 1884

that there was no doubt that Bell was the first to settle this question by experiment.[8] A more recent writer, Dr J. F. Fulton, however, states :

> Though one hesitates to pass judgement upon claims of priority, one cannot doubt that Bell was dishonest and that the chief credit for elucidating the function of the posterior as well as the anterior roots belongs to Magendie. It will be observed that he had clearly in mind the principle of specific nerve energies.[6]

This judgement may be considered harsh. It does appear that Bell's experiments in 1810, published in 1811, were the first, and that they did provide an anatomical basis which had previously not been complete. Certain it is that they inspired Magendie's work. In 1821 Bell's assistant and brother-in-law John Shaw (1792–1827), before his teacher's fame had reached its height there, demonstrated some of the experiments in Paris.[9] In the following year the publication there of the results of Magendie's experiments on a litter of eight puppies [10] proved conclusively that the anterior roots are motor and the posterior ones sensory ; this was further confirmed in the frog by Johannes Müller (1831), in the fish by Wagner (1846) and Stannius (1849), and in birds by Panizza (1834) and Schiff (1858).[11] The fundamental law of neurophysiology which states that a nerve fibre cannot be both motor and sensory should, perhaps, be called the Bell-Majendie Law.

In connexion with the controversy, it may be of interest to quote two Orations. One was delivered in 1843 by James Moncrieff Arnott ; the other in 1935, by Professor Edwin Bramwell. Dr Arnott said :

> There remains to Bell clearly and unequivocally the merit of having first shown that in investigating the functions of the nervous system, we must first direct our attention to the roots and not to the trunks of nerves. That the nervous trunks conveying motion and sensation consist of two distinct sets of filaments in the same sheath. That the filaments for motion form a distinct root from those of sensation ; leaving it to be inferred that the posterior are for sensation . . . And lastly, of having been the first who, dissatisfied with the observation and study of the mere form of the various parts of the nervous system, applied the method of experiment to aid him in determining their function.[12]

In the words of Professor Bramwell he

> . . . formulated a working conception of the nervous system when all was in a state of chaos, a conception which stands today and has served as a basis for all subsequent inquiry and progress.[13]

In 1833 Marshall Hall (1790–1857) introduced the conception of the spinal cord as a chain of segments whose functional units are separate reflex arcs. Marshall Hall's demonstrations of tonic closure of the sphincters by reflex action, of cessation of strychnine convulsions after destruction of the spinal cord, and of the fact that most reflexes are more readily elicited by stimulating the appropriate end-organs rather than their trunks, although appreciated abroad, were for a time the subject of bitter controversy in Britain.[5]

Sir Charles Bell always retained his early love for drawing and painting, in which he had great skill, as shown in his first book on dissections. Paintings which he made of war wounds at Waterloo hang in the Museum of the Royal College of Surgeons of Edinburgh. In 1842, while on a sketching holiday in Worcestershire, Bell died suddenly during the night. He was buried in the village churchyard at Hallow Park.

Alexander Walker had died ten years previously, still convinced that the anterior root was sensory and the posterior one motor.

Laurence Dopson

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1545

PAUL EHRLICH

Dr Johnson straddles English literature partly because he was fortunate enough to have the perfect biographer ; in this respect Paul Ehrlich was also fortunate. When he declared to his friends that for successful work there must be four " G's "—*Geduld, Geschick, Geld und Glück* (patience, ability, money and luck)—Dr Meyer, one of his assistants, replied : " If the first three are present and used properly the fourth " G " comes by itself ". The truth of Dr Meyer's reply will be evident to the reader of Martha Marquardt's book.[1] By his faithful use of the first three " G's " Paul Ehrlich created for himself the fourth " G " ; he provided Martha Marquardt with the opportunity to watch, to work, and to worship, and out of that association has grown a biography which is almost Boswellian in its faithful detail.

PAUL EHRLICH 1854–1915

Acknowledgements to William Heinemann Medical Books Ltd.

To the world at large, Ehrlich is simply the man who discovered salvarsan (606), a cure for syphilis. His claim to fame as a scientist goes much deeper. True, he discovered a number of useful remedies, but so have others whose names are now almost forgotten. Paul Ehrlich was the leader, almost the crusader, in a new branch of medical science which has added to the armamentarium of the practitioner many drugs which are now almost taken for granted as a natural heritage of man. Indeed, looking back to the decades before Ehrlich published his first papers, one wonders what the practitioners did beyond awaiting the natural outcome of a disease ; take away serum therapy, arsenicals, antimonials, basic dyes, alkaloids, sulphonamides and antibiotics, and what is left ?—a bare medical chest, indeed, for the treatment of microbial infections.

Ehrlich's theories on the mode of action of antibodies and drugs were attacked during his own time, and since, on the grounds that they were too naïve or too pictorial ; but it is evident from his own writings, and even more clear from Miss Marquardt's book, that he was endowed with more than an ordinary capacity for visualization of his problems. Although this tempted him to explain his theories in highly pictorial terms, it was also this characteristic which enabled him to direct research in the complex field of organic chemistry and to wed it so successfully to biological research.

[1] For particulars, see p. 394.

The fundamental problem which faces the student of chemotherapy today is selective toxicity. Why is penicillin or chloromycetin able to destroy infecting micro-organisms without showing any appreciable toxicity towards the host cells? We find the problem stated by Ehrlich in somewhat different terms: "It is quite evident that only those substances in which the organotropism and parasitotropism stand in a well-balanced relation to each other can be used in practical medicine as curative substances." It is easy to imagine how excited Ehrlich would have been over the recent discoveries in intermediary metabolisms and comparative biochemistry which begin at last to provide a clue that may solve the riddle.

Interwoven with the picture of Ehrlich the scientist is the picture of Ehrlich the man, and how vivid a picture Miss Marquardt has achieved! She has presented to us an autocrat, intolerant of criticism; a man of childlike simplicity; a lovable, generous and gentle soul devoted with a passionate singleness of purpose to a cause—the cause of science. It would have been easy for Miss Marquardt to gloss over some of the less likeable characteristics of her "chief" and still to have given us a moving picture of a great man; but instead she had the faith that the weaknesses were as essential to a genuine representation of Paul Ehrlich as the rest, and how right she was! This, we feel, is the true likeness of the man, and in its truth still great.

On one point only do I wish to dispute. On page 176 Miss Marquardt states that "606, like all the other substances previously prepared, was invented by Ehrlich *alone*." The italics are not mine. No scientist works in mental isolation; none of his ideas are due to himself alone, particularly when these ideas are worked over by a team such as that which Ehrlich led; and yet after reading this book one wonders, might not Paul Ehrlich himself have made such a claim?

Sir Henry Dale has written a valuable introduction, and while Miss Marquardt makes no attempt to deal with the scientific aspects of Ehrlich's contribution to medicine, she has admirably succeeded in producing a truly fascinating study of the workings of the mind of a great man.

T. S. Work

1546

WILLIAM HARVEY

It is safe to say that more has been said and written about William Harvey than about any other great figure in medicine, save only Hippocrates. Many writers have attempted an evaluation of his contributions to science; the effect of his discovery of the circulation of the blood has been fully studied. The comparatively little material available on the personality of Harvey has now been augmented by Mr Geoffrey Keynes, who has devoted his Linacre Lecture [1] to this subject. Mr Keynes has briefly but skilfully outlined Harvey's career and has at the same time attempted to re-discover his personality by a critical examination of the several portraits in existence, the opinions of Harvey's contemporaries, and the words and acts of the man himself. In discussing the iconography of Harvey, Mr Keynes speaks with authority, for in his Thomas Vicary Lecture for 1948 he gave a full account of the existing portraits, bringing some order to the confusion that had existed regarding them. The present scholarly work is a fitting complement to it and a small but valuable addition to the vast literature on Harvey.

L. T. M.

[1] For particulars, see p. 394.

* * *

MEDICINE

1547 A Synopsis of Medicine

Henry Letheby Tidy. Ninth edition, revised and enlarged. Bristol: John Wright & Sons Ltd., 1949. xx + 1,243 pages 19 × 13 cm. £1 10s. [£1.5]

(i) Specific infectious diseases; (ii) diseases due to physical agents; (iii) the intoxications; (iv) diseases of metabolism; (v) diseases of deficiency; (vi) diseases of the digestive system; (vii) diseases of the circulatory system; (viii) diseases of the respiratory system; (ix) diseases of the kidney and urinary tract; (x) diseases of the blood and spleen; (xi) diseases of the endocrine glands; (xii) diseases of the muscles, joints, and bones; (xiii) diseases of the nervous system. Index.

Of the many synopses available to the English-speaking medical student or postgraduate, "Tidy" holds pride of place. That it does so is due to the fact that it almost certainly contains within its covers more information than any other single-volume textbook of internal medicine. To criticize the new edition seems like sacrilege, but there are a few points which appear to merit discussion. On the diagnostic side, there is indeed little to quibble about. The clinical descriptions of disease are nearly always adequate and often encyclopaedic. The classification is beyond reproach. But it is otherwise with the sections on treatment. The author occasionally enters into the general conspiracy of writers of textbooks on internal medicine to conceal many useful points in modern therapy from the student. Thus, he does not mention surgery for hypertension or for portal cirrhosis; pneumoperitoneum for pulmonary tuberculosis, theophylline in status asthmaticus, and sulphonamide prophylaxis of acute rheumatism are also passed over in silence. The statement that colectomy is contra-indicated in Hirschsprung's disease is diametrically opposed to Aird's experience. One has the impression that colchicine is more frequently used for gout than the older tincture of colchicum, and that phenobarbitone should be mentioned before the bromides in epilepsy. It is not sufficiently emphasized that in thrombo-angiitis obliterans the first thing to do is to stop the patient's smoking. No mention is made of the distinction between granuloma inguinale and lymphogranuloma venereum.

We are sorry to see that the London Hospital work on type I and type II nephritis is ignored, as is the concept of high-output and low-output cardiac failure. Errors are of course very few. We note "Hering-Brewer" for "Hering-Breuer" on p. 643 and 'Harrington" for "Harington" on p. 920.

In conclusion, the reviewer must confess that he has bought the last five editions of this book, which he regards as unrivalled for rapid reference.

S. S. B. Gilder

1548 The British Encyclopaedia of Medical Practice, Including Medicine, Surgery, Obstetrics, Gynaecology and Other Special Subjects. Medical Progress 1948

Edited by *Horder.* London: Butterworth & Co. Ltd. [1948] v + 511 + 28 pages; 5 figures. 25 × 17 cm. £1 10s. [£1.5]

Part I. Critical surveys. (i) Medicine; (ii) surgery; (iii) obstetrics and gynaecology; (iv) paediatrics; (v) cardiology; (vi) chest diseases; (vii) acute infectious diseases; (viii) aviation medicine; (ix) industrial medicine; (x) forensic medicine; (xi) psychological medicine; (xii) tropical medicine; (xiii) chemical pathology; (xiv) progress in vitamins. Part II. Drugs. (xv) Recent developments in pharmacology and therapeutics. Part III. Abstracts. (xvi) Abdominal pain and acute abdominal emergencies—yaws. Index.

For those to whom this annual favourite is unknown, it may be said that it is designed to supplement the information in the encyclopaedia which appeared just before the war. The record of progress is divided into three parts: a series of critical surveys of the most interesting topics of the year, a short section on new drugs, and a selection of abstracts of important articles which have appeared within the previous 12 months. In the present volume, a survey of the abstracting section suggests that no important paper has been overlooked. In the critical surveys, emphasis is on clinical work, and practically every section holds something of interest to the keen general practitioner. Special mention may be made of the brief but informative sections on medical and surgical aspects of hypertension and peptic ulcer, while the physician, surgeon and obstetrician all discuss the problems of thrombosis, with reference to anticoagulant therapy. The sections on paediatrics and cardiology should be of great interest to all clinicians. There is a good discussion of salient advances in aviation medicine since 1941, and an article on forensic medicine in which the writer has wisely not attempted to cover recent literature, but has filled the space at his disposal with hints for the practitioner suddenly forced into the role of forensic expert *malgré lui.*

S. S. B. Gilder

1549 Traité de Médecine. Volumes VIII, X & XI

Edited by *A. Lemierre et al.* Paris: Masson & Cie, 1948. Volume VIII: Maladies du foie et du pancréas. 1,166 pages; illustrations. 25 × 17 cm. 2500 fr. Volume X: Maladies du coeur. 1,167 pages; illustrations. 25 × 17 cm. 3600 fr. Volume XI: Maladies des vaisseaux. 545 pages; illustrations. 25 × 17 cm. 1400 fr.

Volume VIII: Maladies du foie. (i) Sémiologie physique du foie, radiologie hépatique; (ii) exploration fonctionelle du foie. I. Les syndromes hépatiques; (iii) L'insuffisance hépatique; (iv) le syndrome d'hypertension portale; (v) les ictères. II. Maladies hépatiques. (vi) Les foies congestifs; (vii) les cirrhoses; (viii) la maladie de Hanot; (ix) les cirrhoses pigmentaires; (x) les hépatites dégénératives; (xi) les hépatites infectieuses aiguës; (xii) les hépatites toxiques; (xiii) la tuberculose du foie; (xiv) la syphilis hépatique; (xv) les foies parasitaires; (xvi) les abcès du foie; (xvii) les kystes hydatiques du foie; (xviii) les tumeurs du foie; (xix) les affections vasculaires du foie; (xx) la leptospirose à spirochaeta ictero-hemorragiae; (xxi) leptospirose grippo-typhosique et canicullaire. III. Les affections biliaires. (xxii) Moyens d'exploration des voies biliaires; (xxiii) les troubles fonctionnels de la vésicule et des voies biliaires (dyskinésies biliaires); (xxiv) les cholécystites aiguës non lithiasiques; (xxv) les cholécystites chroniques non lithiasiques; (xxvi) la lithiase biliaire; (xxvii) les angiocholites aiguës et chroniques; (xxviii) traitement chirurgical de la lithiase biliaire et de ses complications; (xxix) les cholédocites; (xxx) les cancers des voies biliaires. Maladies du pancréas. (i) Sémiologie du pancréas; (ii) pathologie du pancréas; (iii) indications chirurgicales dans les pancréatites aiguës, chroniques et les tumeurs du pancréas.

Volume X: (i) Examen du cardiaque. I. Sémiologie cardiaque. (ii) Sémiologie cardiaque fonctionnelle et exploration fonctionnelle du coeur; (iii) sémiologie cardiaque clinique; (iv) sémiologie radiologique cardio-vasculaire; (v) la phonocardiographie; (vi) cardiographie et phlébographie en clinique; (vii) électrocardiographie; (viii) troubles du rythme cardiaque. II. Maladies du coeur. (ix) Les cardiopathies congénitales; (x) les cardiopathies acquises; (xi) les endocardites aiguës; (xii) troubles valvulaires chroniques; (xiii) affections du péricarde; (xiv) affections des artères coronaires, les angines de poitrine; (xv) les maladies du myocarde; (xvi) traitement médical des cardiopathies. Les médicaments à action myocardique; (xvii) indications du traitement chirurgical dans les maladies du coeur, du péricarde et des vaisseaux.

Volume XI: (i) Méthodes d'examen et sémiologie vasculaire; (ii) les syndromes d'hypotension artérielle; (iii) l'hypertension artérielle expérimentale; (iv) l'hypertension artérielle. Etude clinique et thérapeutique; (v) traitement chirurgical de l'hypertension artérielle chronique; (vi) les maladies de l'aorte; (vii) maladies de l'artère pulmonaire. Les artérites pulmonaires; (viii) les artérites des membres; (ix) les phlébites des membres; (x) les varices des membres; (xi) les troubles vaso-moteurs et artério-capillaires.

The list of collaborators shows that there are many distinguished contributors to this series and indicates that it has the wide support of French medicine. The printing and production are excellent and the price is much lower than that of similar English and American books. This is a considerable virtue, for no highly priced encyclopaedia is likely to sell nowadays. An encyclopaedia is unavoidably uneven, for the contributors must be numerous, if each is to be expert in his subject; also, it must soon fall out of date, since knowledge advances so rapidly. For these reasons it is tending more and more to be replaced by the review and the monograph.

The only satisfactory way to review an encyclopaedia is to use it for a time as a reference book in one's daily work. When a book is frequently consulted in this way on the actual problems of diagnosis, treatment and teaching, its real value as a tool at the work-bench can be estimated. This test is extremely difficult to apply to the volumes under review because they are not indexed and the tables of contents are not sufficiently informative. This is normal French practice but it seems to be a bad one. Another major difference between this French treatise and Anglo-American literature is the differentiation of variants of diseases as separate syndromes and the preservation of eponyms for these syndromes. If we study any common disease, such as ulcerative colitis or disseminated sclerosis, we find that the course and prognosis vary with such factors as the onset and evolution of symptoms and the particular manifestations. In France there seems to be a tendency to crystallize these different manifestations under special titles, whereas in England we are more impressed by the underlying unity of the disease process. These two factors, the absence of an index and the isolation of unfamiliar

syndromes, make this encyclopaedia difficult reading for an English reviewer.

The difficulties are especially great in volume VIII, which deals with the liver and the pancreas. The opening pages describe methods of examination, including radiology and liver function tests, hepatic insufficiency and portal hypertension. One would have appreciated a more general discussion of the anatomy, physiology and biochemistry of the liver, and its role in health and disease, on lines such as McNee, McMichael and Himsworth have followed in Great Britain. Icterus is described almost entirely in clinical terms and there is repetition of much the same material under icterus and hepatitis. In consequence, newer work, such as the advances in knowledge of haemolytic disease of the new-born and of infective hepatitis, is dismissed too briefly. The recognition of the frequency and importance of " inoculation jaundice " is one of the major discoveries of the last decade, but little is said in this book about the relationship of catarrhal jaundice and infective hepatitis on the one hand and post-arsenical jaundice and serum jaundice on the other, or about the differences in symptoms and severity, the variation in communicability and in infectivity of stools, naso-pharyngeal secretions, etc., or the degree of immunity and cross-immunity conferred. In cirrhosis, it is possible that English and American authors have oversimplified the problem, but no such reproach can be made against this volume, which describes three different varieties of tuberculous cirrhosis, in addition to devoting a chapter to tuberculosis of the liver.

It is a relief to pass on to the later sections, where well-defined pathological entities are clearly described. There is a magnificent account of leptospirosis. In relation to the biliary tracts and the pancreas, there is a full discussion of accessory methods of examination, including not only biliary drainage and cholecystography but also angiocholography and biliary radiomanometry. It is interesting to compare this whole volume with volume III of Bockus' *Gastro-enterology* (1946). Bockus and his collaborators give a much more up-to-date and succinct account of the liver, whereas there is little to choose between the two in relation to biliary tract and pancreas; in fact, one supplements the other.

Volume X contains an account of heart disease on more or less familiar lines. There are excellent accounts of radiology of the heart, electrocardiography and phonocardiography. Angiocardiography and cardiac catheterization are mentioned incidentally but no full-dress discussion of their effect on modern views on the etiology, diagnosis and treatment of heart failure is given. Volume XI contains only 550 pages as compared with over 1,100 in each of the other two volumes. There are full descriptions of vascular hypotension and hypertension, though unilateral renal disease and suprarenal tumours receive less attention than they deserve. Disease of the peripheral arteries is also perhaps treated more briefly than its growing importance merits. This volume is less fully illustrated than volumes VIII and X; throughout the series, the illustrations are of high quality and the radiographs excellently reproduced.

L. J. Witts

1550 Bedside Diagnosis

Charles Mackay Seward. Edinburgh: E. & S. Livingstone Ltd., 1949. xii + 372 pages; illustrations. 19 × 12 cm. 17s. 6d. [£0.875]

(i) Psychogenic symptoms; (ii) some general considerations regarding pain; (iii) head pain; (iv) thoracic pain; (v) epigastric pain; (vi) umbilical pain; (vii) hypogastric pain; (viii) lateral abdominal pain; (ix) anaemia; (x) epistaxis; (xi) haematemesis; (xii) haematuria; (xiii) haemoptysis; (xiv) cough; (xv) dyspnoea; (xvi) tachycardia; (xvii) dysphagia; (xviii) vomiting; (xix) diarrhoea; (xx) jaundice; (xxi) debility and loss of weight; (xxii) pyrexia. Index.

This useful book " was begun in India in 1945 as a distraction from the burden of the day and the heats ", and occupied the spare time of the author for the ensuing four years. Its purposes are to help the medical student in his efforts to develop the art of diagnosis, and to assist the practitioner in so organizing his knowledge that he will bring it the more effectively to bear where it is most needed—at the bedside. The carefully considered plan of the book largely succeeds in gaining these objectives. After a brief introduction, short chapters are devoted to psychogenic symptoms and to general considerations regarding pain. Each successive chapter then deals with a single main complaint or symptom. There is first a synopsis of its possible causes, then a discussion of its physiology and a more detailed consideration of etiology, followed by a discussion of the routine of examination and investigation which should lead to correct diagnosis.

The work underlines the mental processes which should take place in the physician's mind as he considers his case; it serves as a portable guide to differential diagnosis. One can only agree that more mistakes are due to failure to apply knowledge than to ignorance; in helping to guard against such failures the book will have its greatest value. The plan of the book, however, is not without its pitfalls; many diseases must of necessity fall under several chapter headings, and this leads to a plethora of cross-references and an interrupted and repetitive description of the various syndromes. The brevity of the book, a sine qua non of its purpose, exacts its toll of dogmatic statements which perhaps would benefit from qualification. Complaints of the extremities are not dealt with, arthritis is barely mentioned, and the syndrome of the extruded intervertebral disk escapes notice. This is regrettable, in view of the frequency with which the practitioner is confronted with the problem of the differential diagnosis of low back pain.

But these criticisms, after all, are minor; a great deal of useful information has been compressed into small compass, and the book is one to read and use as a practical manual rather than as a work of reference. Certain it is that the practitioner who absorbs and applies its teachings will find his approach to his patients at once more direct and more effective than before; the student will here find the answer to that frequently vexing question, " What should I do, or ask, next? " Dr Seward is to be congratulated on having written a book which should rapidly establish itself as a favourite.

D. F.

1551 An Index of Treatment, by Various Writers

Edited by *Robert Hutchison*, assisted by *Reginald Hilton*. Thirteenth edition. Bristol: John Wright & Sons Ltd., 1948. xi + 972 pages; 100 figures. 25 × 17 cm. £4 4s. [£4.2]

The object of this 40-year-old favourite is clearly set out in the preface. It is designed to supply the practitioner or general handyman of medicine with sound practical advice on the treatment of any condition—medical, surgical, gynaecological or obstetric—with which he may be confronted. For convenient reference articles are arranged alphabetically; they are contributed by a number of well-known British specialists. The advantage of such a book to the more self-reliant practitioner is clear. Where the contributor considers that an intelligent general practitioner could administer the necessary treatment himself, such treatment is described in detail. Where it is obviously beyond his powers, only the principles of therapy are discussed.

The inevitable drawback to such a book is of course the immense difficulty in editing. This drawback is sometimes evident in the present edition. Some contributors have given an excellent up-to-date account of their subject; others have allowed dead wood to remain. Thus, some drugs, such as iron, quinine and purgatives, appear in circumstances which would surprise the modern pharmacologist. It is difficult to believe that iodides arrest hypertrophy of the breasts, or that small doses of quinine help to clear up Eustachian catarrh. Occasionally, a diet recommended bears little relation to present-day food supplies in Britain. A notable omission is the fenestration operation for otosclerosis, which is surely worthy of notice by the most conservative.

Fortunately, the majority of the articles of importance to the general practitioner are full of sound advice. It is difficult to select for praise, but the reviewer was impressed by those on diabetes, mental deficiency, insomnia, the psychoneuroses and anorexia nervosa; on the surgical side the articles on head injuries, fractures, foreign bodies in the air passages, and, of course, the contributions by Hamilton Bailey and Denis Browne, are of the greatest value.

This work, and its companion volume on differential diagnosis, would go far to equipping an isolated practitioner with the knowledge necessary to his efficiency.

S. S. B. Gilder

1552 Early Recognition of Disease

Edited by *Heneage Ogilvie & William A. R. Thomson.* London: Eyre & Spottiswoode Ltd., 1949. (The Practitioner Handbooks.) 134 pages. 22 × 14 cm. 10s. 6d. [£0.525]

(i) Heart disease; (ii) respiratory disease; (iii) neurological disease; (iv) digestive disorders; (v) diseases of the blood; (vi) renal disease; (vii) endocrine disease; (viii) diseases of the eye; (ix) orthopaedic disabilities; (x) non-specific arthritis in adults; (xi) malignant disease; (xii) mental disorders; (xiii) the complications of pregnancy; (xiv) diseases of childhood. Index.

In the early years of medical practice there is a gradual blurring of the sharp outlines of knowledge acquired before qualification; in too many medical careers, symptoms which elicited an almost automatic diagnostic response in the student and house-physician gradually lose their effectiveness as stimuli. Hard-driven, for the most part, and immersed in everyday routine, the general practitioner of ten or a dozen years' standing can avoid or delay this process only by constant revision; and constant revision of the reasonably well-known is a difficult and unrewarding occupation. There is therefore a need for volumes such as this, which presents the views of 15 authorities in less than 125 pages. Each contributor has written a short essay summarizing the facts which should be in the minds of those who see disease in its early stages.

Crighton Bramwell writes on heart disease; his warnings against attributing symptoms to non-existent cardiac lesions in cases of neurocirculatory asthenia are very much to the point, and his statement that even patients with organic heart disease may develop symptoms on a neurotic basis is apposite. The article on neurological disease, by Macdonald Critchley, analyzes the common signs and symptoms attributable to organic disease of the nervous system in very brief compass, and should be of considerable value. The author makes a useful division of these into groups which do not necessarily, which usually, and which almost always, connote organic disease.

The contributions by John F. Wilkinson, "Diseases of the blood", and by Robert Platt, "Renal disease", should be of considerable assistance in differential diagnosis. Ian Lawson Dick and Sir Reginald Watson-Jones have collaborated to produce a useful short article dealing with the more common types of orthopaedic disability, and H. Gardiner-Hill has written on the early diagnosis of the metabolic group of endocrine diseases. There are nine other articles in the symposium which together cover most of the fields with which the general practitioner is concerned.

There is little room for criticism in the case of authors of such calibre, but one feels that the project has been a trifle ambitious for such a small book. Six pages on diseases of childhood by Professor Alan Moncrieff are well worth reading, but one feels that sixty pages would be more appropriate; it is difficult for even such a master to avoid the trite, and impossible, in such brief compass, to develop points worth expanding. The other articles share this handicap of undue brevity. In spite of this, however, there are few general practitioners who would not benefit from perusing this volume. It has, of course, been produced as a Practitioner Handbook and not in any sense as a work of reference.

D. F.

1553 Diseases of Children. Volume II

Edited by *Donald Paterson & Alan Moncrieff.* Fourth edition. London: Edward Arnold & Co., 1949. vii + 1033 pages; 380 figures. 23 × 15 cm. £2

(i) Organic diseases of the nervous system; (ii) functional disorders of the nervous system; (iii) congenital mental defect in childhood; (iv) diseases of the eyes; (v) diseases of muscles; (vi) diseases of bones and joints; (vii) orthopaedic surgery; (viii) medical diseases of the genito-urinary system; (ix) surgery of the uro-genital system; (x) diseases of the liver, gall bladder and pancreas; (xi) diseases of the peritoneum; (xii) rheumatism; (xiii) diseases of the cardiovascular system; (xiv) blood disorders; (xv) infectious diseases; (xvi) venereal disease; (xvii) diseases of the skin; (xviii) malignant disease in children. Index.

The second volume of Garrod, Batten & Thursfield's *Diseases of children*, edited by Paterson & Moncrieff, includes the work of 24 contributors. Fifteen of these are on the staff of the Hospital for Sick Children, Great Ormond Street, London, so that the book represents the teaching of the London Institute of Child Health.

The two volumes of *Diseases of children* comprise the most up-to-date and detailed British textbook of paediatrics available. Vol. II, like Vol. I, is very well produced on good paper, the print is satisfactory, and the clinical photographs and photomicrographs are excellently reproduced. The *x*-ray reproductions, however, as is usually the case, lack definition and detail. The amount of space given to each subject corresponds to its importance: the volume is packed with accurate factual information, and the index is reliable—points of paramount importance in a textbook. From the point of view of the would-be examinee it is regrettable, however, that no clinical photograph could be found to illustrate each of the rarer congenital bone abnormalities mentioned in the text.

Two major criticisms can be made of the book. One is of the references: those given at the end of each chapter are sadly inadequate, often of startling antiquity, and many authors' names, mentioned in the text, are searched for in vain among them.

The second criticism concerns the whole conception of the work. In its present size, it is too detailed for the undergraduate, yet neither text nor references are adequate for a reference book, to be used by the postgraduate student or the specialist. Surely there is room for a really exhaustive, standard British work on paediatrics, to be placed beside the great Continental and American systems.

1554 An Epitome of the Laboratory Diagnosis and Treatment of Tropical Diseases

Horace M. Shelley. Second edition. London: Staples Press, 1949. 147 pages; illustrations. 22 × 14 cm. 10s. 6d. [£0.525]

(i) Examination of the blood; (ii) blood diseases in the tropics; (iii) protozoal diseases; (iv) virus diseases; (v) the dysenteries and liver abscess; (vi) bacterial diseases; (vii) nutrition and deficiency diseases; (viii) climatic diseases; (ix) snake poisons and myiasis; (x) miscellaneous diseases; (xi) diseases due to fungi; (xii) diseases due to helminths; (xiii) compendium of drugs; (xiv) laboratory notes. Index.

This book is meant to "supply the busy practitioner of medicine in the tropics with simple details concerning the essentials of laboratory diagnosis and the treatment of diseases common to those climes. All mention of symptomatology and clinical signs is avoided . . ." This unusual combination of pathology and treatment is worked out in 14 very short sections, including those on examination of the blood, blood diseases in the tropics, protozoal diseases, virus diseases (this includes Bartonella infection), the dysenteries and liver abscess, bacterial diseases, nutrition and deficiency diseases, climatic diseases, snake poisons and myiasis (an odd mixture), miscellaneous diseases, diseases due to fungi and diseases due to helminths (in which are included lambliasis and balantidiasis !). Laboratory notes include a list of requirements for the establishment of a small laboratory.

Some of the accounts of laboratory procedures are clear and straightforward and may be useful to general practitioners who have to do their own clinical pathological investigations. The rough sketches accompanying certain sections are, however, very crude and serve no useful purpose. The notes on the interpretation of results are sometimes misleading, and there are many points on which the reader may find himself in conflict with the author. For instance, Giemsa or Leishman stains only are recommended for staining blood-films in malaria. Rapid methods of staining now in common use, such as Field's, are referred to in the section on examination of the blood, but not in that on malaria. There is no mention of the importance of serological reactions in the diagnosis of yaws, or of serial serological examination for immune bodies in cases of suspected yellow fever. The details of the cultivation and differentiation of dysenteric bacilli are surely outside the stated scope of the book, quoted in the first sentence of this review. Needling of an amoebic abscess as a method of diagnosis is recommended, apparently without reserve. The inclusion on p. 104 of "Increase of haemoglobin to 110 with polycythaemia" as a pathological feature of "heat stroke" is thoroughly misleading and not accompanied by any explanation or qualification.

The sections on treatment are not always easy to follow, and the advice given may be questioned in places. The author's statement regarding paludrine is quoted: "It is considered superior to all other anti-malarial remedies and a single dose of 100 mg. has proved efficient in stopping clinical attacks of malignant tertian and benign tertian malaria." The dosage of mepacrine recommended for the treatment of the "uncomplicated case of acute malaria" (species unspecified) is lower than that in general use.

In blackwater fever the author recommends that "the patient should imbibe large quantities of fluid . . ." He does not stress the importance of maintaining a fluid balance, and the dangers of excessive fluid intake are not mentioned. Judging by his further recommendations in the treatment of blackwater fever, the author

does not adhere to any of the modern views of its pathogenesis. Twenty grains of sodium bicarbonate given every two hours during the first day (in Sternberg's mixture) " . . . renders the urine alkaline." Caffeine sodium citrate " can be used as a diuretic. " Finally: " Antimalarial remedies should be withheld, for the damage has already been inflicted and at this stage the ordinary remedies are useless." The reviewer disagrees on every count, and believes he is in good company. Alkali will not always render the urine alkaline, particularly when the kidneys are already damaged; ordinary diuretics are of no value; antimalarial drugs other than quinine must be used if parasites are present in the peripheral blood.

B. G. Maegraith

1555 Bright's Disease

Henry A. Christian. New York: Oxford University Press; London: Geoffrey Cumberlege, 1948. (Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.) vi + 385 + 13 pages; 40 figures. 24 × 16 cm. £2 5s. [£2.25]

Part I. General considerations. (i) Introduction; (ii) historical; (iii) normal renal structure and function; (iv) protein in urine (albuminuria); (v) casts and cells in the urine; (vi) blood chemistry; (vii) etiology; (viii) pathogenesis of renal lesions of Bright's disease; (ix) pathology; (x) pathological physiology; (xi) method of examining the patient with Bright's disease; (xii) clinical classification. Part II. Clinical aspects. (xiii) Introduction; (xiv) acute Bright's disease; (xv) acute Bright's disease, hemorrhagic type or type without nephrotic syndrome (acute hemorrhagic Bright's disease); (xvi) acute, subacute and chronic edematous Bright's disease, nephrotic type (nephrotic syndrome of Bright's disease); (xvii) subacute and chronic hemorrhagic Bright's disease; (xviii) chronic non-edematous Bright's disease; (xix) certain special syndromes of Bright's disease. Bibliography. Index.

In this book the distinguished Professor of Medicine at Harvard University gives his mature views on diseases of the kidney, which has been his principal subject of study for 47 years. There is a preliminary section of 138 pages which deals competently with the anatomical, pathological and physiological problems. Of special interest is the method of classification of nephritis. This is based on clinical rather than pathological and etiological criteria. It is not claimed that it is ideal but that it has the advantage of ease for clinical use and foretells with considerable accuracy how the disease will progress. The main divisions are: (i) acute Bright's disease, haemorrhagic type or type without nephrotic syndrome; (ii) acute, subacute and chronic oedematous Bright's disease, nephrotic type; (iii) subacute and chronic haemorrhagic Bright's disease, and (iv) chronic non-oedematous Bright's disease. The text indicates that division (i) includes substantially all acute cases with or without oedema, the cases in division (ii) being subacute or chronic. This classification obviously cuts across the pathological basis to which we are accustomed.

Each section contains a number of illustrative cases reported in sufficient detail and so clearly that one can readily visualize the clinical appearance. It is of interest to observe how closely these cases fall into the appropriate division of the system of classification adopted. It might be unwise for an unqualified student in Great Britain to follow this method of classification. But to the postgraduate student, or to those who pay special attention to nephritis, the book is of the highest value. The statements in the text are based on a lifetime of study and observation. Any intelligent reader can reclassify the types as he pleases without affecting the material presented in the pages.

The text is clearly written and is easy to read and comprehend. The printing and paper are good, though there is a misprint on page 640 (3). The price seems somewhat high.

Henry Tidy

1556 Arterial Hypertension

David Ayman. Edited by *Henry A. Christian.* New York: Oxford University Press; London: Geoffrey Cumberlege, 1948. (Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.) iv + 93 + 2 pages. 24 × 16 cm. 12s. 6d. [£0.625]

(i) Introduction; (ii) history; (iii) etiology; (iv) pathological physiology; (v) pathology; (vi) constitutional type in hypertension; (vii) symptoms; (viii) evolution of essential hypertension from earliest stages; (ix) physical findings; (x) X-ray studies; (xi) electrocardiograms; (xii) other laboratory data; (xiii) differential diagnosis; (xiv) treatment. Bibliography. Index.

The experience of the last 15 years in the experimental production of hypertension in laboratory animals, and in the efforts to treat hypertension in man by such drastic procedures as lumbodorsal sympathectomy, has led to a tremendous advance in our fundamental ideas of the nature of this most important, common, and intriguing condition. For those practitioners who wish to understand the modern outlook the monograph under review will form an excellent primer. It is impossible in some ninety pages to cover the whole subject of hypertension adequately. Dr Ayman succeeds, however, both in giving a balanced account of some of the more outstanding contributions to knowledge in recent years and in conveying appropriate instructions for the investigation and care of the hypertensive patient. The reader will find in this book full accounts of the part played by heredity, the nervous and psychological make-up of the patient, and the more measurable underlying organic faults such as the Goldblatt kidney and varied endocrinological disturbances. Body-build, racial factors, and the like are all given their proper place.

One or two matters of practical management, however, may seem strange to British readers. The author has been partly responsible for the habit of instructing patients, or members of their family, to take their own blood-pressures, and in one section of the book there is considerable discussion of the value of these " home readings ". We should doubt whether such efforts on the part of the patient are for his benefit. In certain susceptible individuals they would undoubtedly do a great deal to increase the apprehension and misery of the patient. Sympathectomy is critically reviewed but the author is obviously a little biased in its favour. Taken by and large, this procedure has been a disappointing one, and we still do not know how to select the occasional case which admittedly does have a favourable response to the operation. Ayman thinks that the operation may do good even if it only abolishes the rises of blood-pressure which occur with emotion and excitement. The rice diet is discussed somewhat briefly, but perhaps this is of little importance, as enthusiasm for this line of therapy is as likely to wane with the years as enthusiasm for sympathectomy. It is curious to see it included under the heading of " Ineffectual forms of treatment ". Treatment with potassium thiocyanate is recommended. A good deal of trouble has to be taken to control the blood-levels of this substance and it seems doubtful if the gain is worth the effort.

These, however, are minor criticisms in what is a useful and well-balanced monograph. We must admit that there is as yet no satisfactory treatment for this distressing condition and whatever line is taken by an author in a clinical publication is always open to easy attack. Dr Ayman has succeeded well in his task and no doubt when he writes the section again for a future edition the instructions on the care of patients will differ widely from those which are given in the present monograph.

J. McMichael

1557 An Introduction to Cardiology

Geoffrey Bourne. London: Edward Arnold & Co., 1949. viii + 264 pages; 65 figures. 22 × 14 cm. 18s. [£0.9]

Section I. Examination of the heart. (i) History-taking and physical examination; (ii) special methods of investigation. Section II. Heart failure. (iii) The nature of heart failure; (iv) the symptoms of heart failure; (v) the signs of heart failure; (vi) the treatment of heart failure. Section III. The myocardium. (vii) Diphtheritic myocarditis; (viii) rheumatic carditis; (ix) myocardial degeneration; (x) the thyroid gland and heart disease; (xi) the heart in anaemia. Section IV. Cardiac disorders and irregularities. (xii) Premature beats; (xiii) paroxysmal tachycardia; (xiv) auricular flutter; (xv) auricular fibrillation; (xvi) heart block; (xvii) bundle-branch block. Section V. Pericardial disease. (xviii) Acute pericarditis; (xix) chronic pericarditis. Section VI. Valvular disease. (xx) Mitral disease; (xxi) aortic regurgitation; (xxii) aortic stenosis; (xxiii) disease of the tricuspid valve; (xxiv) congenital heart disease; (xxv) malignant endocarditis. Section VII. Vascular disease and the heart. (xxvi) The effects of arteriosclerosis upon the heart; (xxvii) hypertensive heart disease; (xxviii) cardiac infarction; (xxix) angina of effort; (xxx) left submammary pain and angina innocens; (xxxi) cor pulmonale; (xxxii) aneurysms. Section VIII. (xxxiii) The heart in pregnancy; (xxxiv) effort syndrome; (xxxv) cardiac signs in symptom-free young adults; (xxxvi) cardiac symptoms and signs in general medical diseases. Index.

This book is written for those who are relatively inexperienced in cardiology. Dr Bourne has aimed at providing a sound working knowledge and has wisely refrained from including the more specialized methods of investigation. Heart failure remains the central problem, and a readable and balanced account of this occupies four chapters. Individual disorders are methodically presented, and the scheme adopted should induce a good approach at the bedside. Use of the term " myocardial degeneration " as a clinical entity is perhaps open to criticism since it is but rarely the dominating factor. Among the best chapters is that devoted to the difficult subject of the heart in thyroid disease. It may be added,

however, that thyroid extract sometimes fails to alleviate angina in myxoedema, and may even render it more severe. Conduction defects and arrhythmias are illustrated by well-chosen electrocardiograms, a minor omission being the chest lead changes in bundle-branch block. There is sound advice on the recognition of pericarditis in all its forms, but not all cardiologists would consider auricular fibrillation a deterrent to operation in constrictive pericarditis.

Turning to mitral disease, the author firmly supports the contention that stenosis and incompetence, though often co-existing, are clinically separable entities. He considers mitral regurgitation alone to be relatively innocuous, and attributes eventual heart failure to weakening of the left ventricle by the original disease. Aortic valve disease is well portrayed, and the important point is made that both thrill and murmur of aortic stenosis may disappear with the advent of failure. There is an excellent chapter on congenital heart disease, which reflects the increased importance of the subject. Writing of hypertension the author considers that raised blood-pressure by itself produces no deleterious effect on the heart, but that with added coronary atheroma and myocardial degeneration the already hypertrophied left ventricle becomes rapidly enlarged. From the clinical view-point, however, many cardiologists would consider hypertrophy as evidence per se of heart disease, and some would correlate its degree with the duration of failure. There is a very useful section on the management of these difficult cases. Triple rhythm in the early stages of cardiac infarction would have deserved mention; though not invariable, it is valuable evidence when an electrocardiogram is unobtainable. A diagram showing the sites for routine chest leads would usefully supplement the text, which is somewhat misleading with regard to leads 5 and 6.

Dr Bourne writes in the scholarly style which we have come to expect from him, often illustrating his remarks with novel analogies and striking case examples. Although his views are occasionally unorthodox, he has succeeded in supplying both stimulus and basis for a fuller knowledge of the subject.

Robert Benson

1558 Cardiology

William Evans. London: Butterworth & Co. Ltd., 1948. xi + 310 + 20 pages; 269 figures. 25 × 17 cm. £1 15s. [£1.75]

(i) History taking and physical examination; (ii) heart sounds and murmurs; (iii) cardiac enlargement; (iv) arrhythmia; (v) congenital cardiovascular disease; (vi) diseases of the pericardium; (vii) endocarditis; (viii) aortitis; (ix) cardiac pain; (x) hypertension; (xi) the heart in disease of the lungs; (xii) heart failure; (xiii) heart disease and pregnancy; (xiv) the heart in endocrine disorders; (xv) the heart in miscellaneous conditions; (xvi) other vascular diseases and effects; (xvii) the life and livelihood of patients with heart disease. Index.

No fewer than 11 new textbooks on heart disease have appeared in English since 1947. Several of these have been inspired, if the word may be used in a broad sense, by an author's preoccupation with his own particular cardiological interests, others by a dissatisfaction with the previous form or technique of presentation of the subject. Many of them have seen the light of day on the most slender pretexts, and presumably are sustained by the allegiance of the medical school where they originated. Dr William Evans' book will not find itself in such company. Its content and form of presentation are not stereotyped and, time and again, new view-points of well-worn subjects are put forth with quiet candour. So often do they skirt the supposedly unorthodox that the casual reader may find himself at times doubting Dr Evans' words. However, one feels that this book was not written for the casual reader, and that a few of the rather unusual statements are thought-provoking, somewhat disturbing to one's own complacency, and certainly a stimulus to more careful clinical observation in the future. The author is perhaps at his best when he is quietly tilting against time-honoured methods of teaching.

The reviewer was visiting the United States when the first copies of the present book reached that country. He recalls the astonishment that greeted Dr Evans' definition of a raised blood-pressure, namely "... when the systolic pressure is 180 or over, and/or the diastolic pressure is 110 or over ... and in the presence of clinical, radiological and cardiographic evidence of cardiovascular hypertrophy." These figures, even higher than the usually accepted levels in this country, were little short of startling in the United States, where a blood-pressure of a few millimeters greater than the sacrosanct 150/90 is regarded as quite a serious matter.

Acquaintance with Dr Evans' refreshing methods of teaching clinical cardiology to students and postgraduates will help in understanding the underlying philosophy of his book. There is much to praise in it and a little to criticize. He sounds a well-timed warning against what he calls "unwarranted cardiac invalidism", and this healthy advice re-echoes throughout the book. He rightly identifies auricular flutter with auricular tachycardia, but no mention is made of ventricular tachycardia. An unfortunate emphasis is laid on mean axis deviation in the electrocardiogram and as a result the more important signs of ventricular hypertrophy tend to be overlooked. This defect is clearly shown in an electrocardiogram of congenital subaortic stenosis (fig. 112) described as showing right axis deviation; it deserved the additional comment that chest leads would have demonstrated left ventricular hypertrophy. No mention is made of the value of chest leads in bundle branch block.

Since the book is addressed to medical students and general practitioners, a detailed account of recent advances in haemodynamics, cardiac catheterization or angiocardiography is not called for. One would have supposed, however, that the use of penicillin in cardiovascular syphilis would deserve mention either in support or condemnation and that dicumarol was promising enough to warrant more than six words.

In this book, medical students and general practitioners will find emphasis laid on the facets of heart diseases which concern them and will read and refer to it with profit. The selection and high quality of reproduction of the figures and especially of the teleradiograms are a credit to the author, the medical technicians and the publisher.

W. S.

1559 Cardiovascular Disease in General Practice

Terence East. Third edition. London: H. K. Lewis & Co. Ltd., 1949. x + 208 pages; 34 illustrations. 22 × 14 cm. 15s. [£0.75]

(i) The interpretation of symptoms; (ii) physical examination of the heart; (iii) heart failure; (iv) the treatment of heart failure; (v) failure of the coronary circulation; (vi) peripheral failure; (vii) the infections of the heart; (viii) subacute bacterial endocarditis; (ix) cardiovascular syphilis; (x) chronic valvular disease; (xi) pericarditis; (xii) hypertension; (xiii) thyrotoxicosis; (xiv) auricular fibrillation and flutter; (xv) ectopic disorders of rhythm; (xvi) disorders of conduction; (xvii) the cardiovascular system in anaemia, chronic pulmonary disease, chronic renal disease, minor infections, anaesthesia, pregnancy, athletics, deficiency conditions; (xviii) diseases of arteries and veins; (xix) congenital diseases of the heart; (xx) the heart in middle age and onwards; (xxi) some aberrations and the normal heart. Index.

There have been so many advances in cardiology during the past few years that the author has rightly decided to bring out a 3rd edition of this useful aid to general practitioners. The 2nd edition was published in 1946[1]. The new material is found chiefly in the sections on heart failure, ischaemic heart disease, high blood-pressure, congenital heart disease, pulmonary heart disease and thyrotoxicosis. Nevertheless, there are still no details of the low sodium diet, which is certainly the most important advance in the treatment of heart failure; the only practical change in the management of cardiac infarction is the selection of cases suitable for anticoagulant therapy, and this is not discussed; some information concerning the value of penicillin in the treatment of cardiovascular syphilis would have been welcome; the picture of pulmonary heart disease is not convincing, and essential points such as signs of vasodilatation, the difference between central and peripheral cyanosis, the masking effects of emphysema on the second heart sound, and the frequency of coincidental hypertension are not mentioned; in the treatment of thyrotoxicosis one is left with the impression that methyl thiouracil has practically replaced surgery, and that the general practitioner might well carry out the whole of the treatment himself—a view that may well be maintained by the author with some justification, but not one about which there is wide agreement; some further comment on the general therapeutic problem would not have been out of place.

These are criticisms of the newer work that has been incorporated in the book, and detract little from its original value, which was in the successful presentation of the elements of cardiology to the busy practitioner in the simplest and shortest way. To cover so much ground in 200 pages, omitting little of practical importance, apart from what has been mentioned above, is very commendable. The absence of electrocardiograms and *x* rays does not matter, because their interpretation should be left to the specialist.

Paul Wood

[1] For review, see *BMB* **1151**.—Ed.

1560 B.C.G. Vaccination in Theory and Practice

K. Neville Irvine. Oxford : Blackwell Scientific Publications, 1949. xiii + 130 pages. 22 × 14 cm. 9s. 6d. [£0.475]

(i) History ; (ii) the theory of vaccination ; (iii) the production of the vaccine ; (iv) variation in the virulence of B.C.G. ; (v) virulence experiments in animals ; (vi) the safety of B.C.G. vaccination for man ; (vii) the resistance produced in animals ; (viii) the resistance produced in man ; (ix) the technique of vaccination ; (x) a world survey of B.C.G. vaccination ; (xi) discussion. Index of authors. Subject index.

Dr Irvine has produced an extremely useful and compact little book and, despite the great amount of matter condensed in its pages, he has contrived to make it clear and convincing. The lay-out is good, and the evidence offered for and against the different aspects of BCG theory and practice so clearly and compactly set forth that interest leads the reader on from chapter to chapter.

After mentioning other attempts to confer immunity, Dr Irvine outlines the evolution of BCG vaccine, the methods of its preparation and the theory behind its use. He summarizes the evidence for believing that the strain may be less virulent now than before 1930 owing to the dying out of the " S " variants, and discusses the possible attenuation of the strain in the future. His summary of the reasons for believing that present-day BCG is harmless is convincing. The weight of evidence he produces for considering that BCG confers immunity is fairly conclusive, though this must vary considerably in different populations and age-groups. As he says, any increase in immunity is better than none. His chapter on technique of vaccination is most useful.

In some of Dr Irvine's comparisons of morbidity rates in patients vaccinated and in control cases one is doubtful whether those developing " pulmonary tuberculosis " all had post primary lesions or merely the primary infection. Dr Irvine can, of course, only quote the literature as published. His discussion as to whether those vaccinated should be segregated or not, both before and after vaccination, is useful. He recommends the former, but the chest physician in Britain, at least, will find that the necessity for segregation will greatly reduce the number of contacts he can vaccinate. The difficulty is not only in arranging for segregation but in ensuring that a sufficient number are segregated at the same time, so that a BCG vaccination session becomes profitable. This is a most important point and the proper solution is the widespread boarding-out of contacts by local authorities and, preferably, the establishment of BCG teams.

Incidentally, for the help of those reading this book, Dr Irvine uses the term tuberculin " inversion ", instead of tuberculin " conversion ", in discussing tuberculin skin tests.

E. Aslett

1561 Die Tuberkulose des Kindes. Ein Lehrbuch aus der Kinderheilstätte, Wangen im Allgäu

Heinrich Brügger, Reiner W. Müller & Maria Birkenfeld. Stuttgart : Georg Thieme, 1948. viii + 340 pages ; 209 illustrations. 25 × 18 cm. 16 Mk.

(i) Allgemeines über die Tuberkulose-Infektion und -Krankheit ; (ii) allgemeine diagnostische Hilfsmittel ; (iii) die endothorakale Tuberkulose des Kindes ; (iv) die Tuberkulose im Bereich des Halses und des Bauches ; (v) Tuberkulose des Skelettsystems und der Weichteile ; (vi) Hauttuberkulose. Index.

This textbook is designed to cover the whole of the subject of tuberculosis in children. Dr Brügger, who has evidently had long experience in his sanatorium for children at Wangen in southern Württemberg, is the editor and main contributor. Emphasis is laid on the general nature of the tuberculous disease process in childhood and the fact that it is seldom entirely confined to one part of the body. These facts are constantly kept before the reader and, in spite of the triple authorship, the book is successful in maintaining continuity and balance in the subject-matter and in avoiding needless repetition. Advances made in the post-war years receive no mention. This is hardly surprising, as, although published in June 1948 the book was completed in October 1946 and the authors had no access to foreign literature after 1939. The omissions are naturally most noticeable in the sections on therapeutics ; under the heading of chemotherapy, only gold is mentioned (and, incidentally, condemned). BCG inoculation, not carried out in Germany since the Lübeck disaster, is considered shortly but with approval.

In his opening section, Dr Brügger clearly sets forth the generally accepted views on the natural history of tuberculosis. The section on diagnostic measures contains a particularly useful and comprehensive account of the methods of tuberculin tests and their significance. Over one-third of the book is devoted to primary intrathoracic tuberculosis, its complications, prognosis and treatment. Although the important part played by the complication of atelectasis is recognized, the reader is left wondering if some of the radiograms of the " benign perifocal infiltrations " do not really represent the former condition. For instance, fig. 20 might well be a collapse of the lateral segment of the right middle lobe and, in this connexion, it is unfortunate that for 40 anteroposterior radiograms of the benign infiltrations and atelectases there are only four lateral views. Again fig. 128, illustrating " basal triangles " in pertussis, appears to represent bilateral basal collapse. There is no mention of the treatment of atelectasis by bronchoscopic suction and the rarer condition of obstructive lobar emphysema is not discussed. In the section on differential diagnosis, insufficient attention is paid to the question of collapse of non-tuberculous origin and a second edition will, no doubt, devote more space to the differential diagnosis of tuberculous meningitis, now that its early recognition has become so important. Adult-type tuberculosis in children is fully considered.

Dr Müller gives excellent accounts of the clinical findings and course of tuberculosis of the neck and abdomen. The section on tuberculous disease of the skeletal system is well arranged and Dr Birkenfeld's accurate descriptions of the clinical findings in tuberculous infections of individual bones and joints are particularly good. She rightly lays stress on the importance of early recognition of skeletal involvement. This treatise is obviously based on the author's very considerable experience and wide reading. Where a description of some infrequent manifestation is not based on personal observation, this is clearly stated. One is left with the impression that the authors are not only experienced in the subject of tuberculosis but are also good paediatricians, well understanding the difficulties of diagnosis and of prolonged hospital treatment in young children.

Most of the 209 illustrations are positive reproductions of radiograms and, though varying in quality, are for the most part as good as the paper permits and clearly demonstrate what is required. The text is interspersed with many illustrative case histories. There are 278 references, mostly to German works. The print is clear and the language not too circumlocutory.

The reviewer has no hesitation in commending this book, not only to senior students and trainee paediatricians, but also to physicians working in this branch of medicine.

J. P. M. Tizard

1562 Ankylosing Spondylitis : a Practical Guide to its Diagnosis and Treatment

F. Hernaman-Johnson & W. Alexander Law. London : Butterworth & Co. Ltd., 1949. viii + 200 pages ; 41 figures. 22 × 14 cm. £1 5s. [£1.25]

Part I. (i) The spondylitic syndrome ; (ii) aetiology and pathology ; (iii) clinical diagnosis ; (iv) radiographic diagnosis ; (v) some reflections on treatment ; (vi) X-ray treatment ; (vii) vaccines ; (viii) gold, bismuth and arsenic ; (ix) thorium X ; (x) general management of patients with spondylitis ; (xi) mental factors : occupation, sex and marriage ; (xii) cortisone and pregnenolone in the treatment of " rheumatism," including spondylitis ; (xiii) concluding remarks. Part II. (xiv) Conservative treatment ; (xv) correction of the spinal deformity by osteotomy of the spine ; (xvi) hip joint reconstruction by vitallium mould arthroplasty ; (xvii) surgical treatment of joints less frequently involved in ankylosing spondylitis. Index.

This small monograph deals with the subject of ankylosing spondylitis from the somewhat doctrinaire point of view which is associated with the Charterhouse Rheumatism Clinic, of which the late Dr Hernaman-Johnson was physician. The " wide-field " technique of *x*-ray treatment is recommended in preference to the more commonly accepted " deep " technique, although it is said : " It must be admitted that, in Great Britain, the wide-field method has made little progress." The next method of attack upon the disease to be discussed is the use of vaccines, a procedure which the author admits to be " purely empirical ", and one which has lost favour with other schools of rheumatological thought.

In the following chapter the use of gold salts, bismuth and arsenic is advocated. It is claimed that the first " almost deserves the name of a specific "—a view which is very far from representing the general opinion in this or any other country at present. Finally, the use of thorium X is recommended with enthusiasm. The author's remarks on the general management of patients with spondylitis are sensible and wise, and he has managed to include a brief chapter on cortisone and its relations.

Mr Alexander Law contributes the last four chapters, on the surgical treatment of the effects of ankylosing spondylitis, and this section will be read with interest and profit by all who are engaged in this field.

W. S. C. Copeman

1563 Surface and Radiological Anatomy: for Students and General Practitioners

Originally written by A. B. Appleton, W. J. Hamilton & Ivan C. C. Tchaperoff. Third edition by *A. B. Appleton, W. J. Hamilton & G. Simon.* Cambridge: W. Heffer & Sons Ltd., 1949. viii + 332 pages; 390 figures. 25 × 19 cm. £1 15s. [£1.75]

General anatomy and methods. The upper limb. (i) Shoulder and arm; (ii) elbow, forearm and hand; (iii) vessels and nerves. The chest and back. (iv) Thoracic wall; (v) thoracic contents; (vi) physical examination of the thorax; (vii) great vessels; (viii) oesophagus. Abdomen. (ix) Abdominal wall; (x) physical examination of the abdomen; (xi) abdominal contents; (xii) perineum; (xiii) deep blood-vessels of the abdomen. Head and neck. (xiv) General features; (xv) the neck; (xvi) special organs and regions; (xvii) vessels and nerves; (xviii) the brain and its associated vessels; (xix) radiology. The vertebral column. The lower limb. (xx) Buttock and thigh; (xxi) region of the knee; (xxii) leg and foot; (xxiii) vessels and nerves. Index.

It is doubtful whether any single textbook can cover so wide a field as surface anatomy and radiological anatomy and yet meet the needs of both students and general practitioners. No one has yet succeeded in combining the best of the material in the textbooks of surface anatomy as they existed in the pre-Röntgen days with the best of the material in the books on radiology.

The most concentrated and precise presentation of surface anatomy was that of the late Sir Harold Stiles of Edinburgh, and this was first published as the last section of Cunningham's *Textbook of anatomy* in 1902. The most extensive and accurate presentation of radiological anatomy in any language is Alban Köhler's *Röntgenologie*, translated into English by A. Turnbull. The first German edition appeared in 1910 and the first English translation, of the 5th edition, was published in 1928. Köhler, by a stroke of genius, supported by incomparable clinical experience, gave the first and only clear survey of the borderlands of normal and of early pathological conditions in the radiograph. The combination of anatomy and radiology as presented by Stiles and Köhler is still unapproached, and most difficulties can be solved by reference to the one or the other.

The book under review contains a mass of detailed information of use to the student, but lacks any statement of those general principles which allow the student to organize the detail into a concrete whole. The anatomical illustrations are of the high quality expected from such a competent medical artist as A. K. Maxwell. The radiographs are well selected but their reproduction still leaves much to be desired. A well-reproduced radiograph demands a paper of photographic quality and this involves much expense.

The more recent techniques of tomography, ventriculography and pneumatization are presented in detail. A brief statement of the qualities of an adequate radiograph of any part of the body might be of help to the student, for it is the radiograph itself rather than any printed reproduction of it which gives the maximum information.

H. A. Harris

1564 Neuroradiology

Alexander Orley. Oxford: Blackwell Scientific Publications, 1949. xii + 421 pages; 572 figures. 26 × 18 cm. £3 3s. [£3.15]

(i) Radiography of the skull; (ii) radiography of the temporal bone; (iii) sphenoidal sinuses; (iv) the sphenoidal fissure; (v) cranial foramina; (vi) tomography; (vii) cranial deformities; (viii) head injuries; (ix) lesions of the cranium; (x) changes in the skull associated with systemic diseases; (xi) asymmetry of the skull; (xii) radiographic changes in the feeble minded; (xiii) non-pathological intracranial deposits of calcium; (xiv) displacement of calcified normal intracranial structures by space occupying lesions; (xv) pathological intracranial calcification other than neoplasms; (xvi) degenerative conditions in which abnormal intracranial calcification is usually absent; (xvii) increased intracranial pressure; (xviii) cranial and cerebral circulation; (xix) vascular tumours and anomalies of the brain; (xx) cerebral angiography; (xxi) arteriography in lesions of the blood vessels; (xxii) diagnosis of the histological structure of tumours from the angiogram; (xxiii) peripheral arteriography; (xxiv) cerebral neoplasms; (xxv) lesions and deformities of the sella turcica and parasellar lesions; (xxvi) meningioma; (xxvii) acoustic nerve tumours; (xxviii) congenital tumours; (xxix) tumours of the blood vessels of the brain; (xxx) metastatic tumours; (xxxi) calcified tuberculoma of the brain; (xxxii) intracranial abscess; (xxxiii) air studies of intracranial lesions; (xxxiv) interpretation of the normal ventriculogram; (xxxv) ventricular measurements; (xxxvi) different radiographic projections used in ventriculography; (xxxvii) encephalography; (xxxviii) ventricular changes following head injury; (xxxix) porencephaly; (xl) arachnoiditis; (xli) encephalography in cases of mental deficiency and epilepsy; (xlii) ventriculography; (xliii) lesions and anomalies of the spine and spinal cord; (xliv) spinal injuries; (xlv) posterior prolapse of the intervertebral disc; (xlvi) spinal tumours; (xlvii) forecast of the histological nature of the tumour from radiographic evidence; (xlviii) myelography; (xlix) neuropathic disturbances. Bibliography. Index of authors. Index.

The author states that the greater part of the material on which this book is based was collected during the war of 1939–45. The field of neuroradiology during this period in Britain was somewhat restricted because of the divorce from free contact with the work in progress in other countries. This book reflects the situation. The author has read widely in his subject, as the very complete bibliography witnesses. It must, however, be realized that the material of the book and the opinions expressed therein are far behind present-day thought and methods.

The section on cerebral angiography is an outstanding example. The contrast material advocated is considered by most workers to be dangerously radioactive. The open method of injection described has been abandoned, in other than exceptional cases, in the percutaneous technique. The reproductions of angiograms are for the most part poor and cover little of the field of demonstrable abnormalities.

The technique of positioning in ventriculography is well described, but in the section on abnormal ventriculographic findings only four projections are used in the diagrams. The art of ventriculography lies in suiting the technique in each case to the initial findings, in order fully to demonstrate the lesion for the guidance of the neurosurgeon. There is little suggestion of the importance of this. The section on the technique of myelography is headed most misleadingly "Lumbar encephalography". Some of the statements which follow would be regarded as dubiously accurate by the majority of experienced workers in this field, and no mention is made of the possible use of opaque media other than iodized oil.

The standard of production of the book is high and it is the greater pity that some of the radiographs reproduced, notably those on pages 101–103 and 120, fail to demonstrate to the reader the conditions described. In the section on radiography of the temporal bone there are full instructions for radiographic procedure, though the standard American and Swedish projections are ignored, while adequate anatomical explanation of the resulting radiographs is not given. The format of this book is excellent, but the subject deserves a volume of much greater size and scope, and a wider basis in material. In the last 15 years this specialized field in radiology has produced evidence which has greatly influenced thought and procedure in neurology and neurosurgery. Technique has advanced rapidly in the past five years, and it was perhaps inevitable that, by the time the book was published, some of the statements in it should be behind current opinion.

1565 A Descriptive Atlas of Radiographs. An Aid to Modern Clinical Methods

A. P. Bertwistle. Seventh edition, revised and enlarged. London: Henry Kimpton, 1949. xxx + 622 pages; 980 illustrations. 26 × 18 cm. £2 10s. [£2.5]

(i) Radio-diagnosis; (ii) cancer campaign; (iii) X-ray museum; (iv) the clinical application of radiology; (v) X-rays in the diagnosis of internal disease; (vi) milestones in radio-diagnosis; (vii) silhouette radiograph process; (viii) normal bones and epiphyses; (ix) congenital abnormalities; (x) fractures; (xi) diseases of bones; (xii) tumours of bone; (xiii) injuries and diseases of joints; (xiv) nasal system; (xv) dental system; (xvi) alimentary system; (xvii) urinary system; (xviii) respiratory system; (xix) nervous system; (xx) vascular system; (xxi) ductless glands; (xxii) female generative system; (xxiii) muscles; (xxiv) medico-legal; (xxv) embryology; (xxvi) anthropology; (xxvii) helminthology; (xxviii) occupational diseases. Index.

The compiler of an atlas of radiographs who wishes to limit himself to one volume must always be faced with the problem of deciding on those examples which must be included and those which can be excluded. To be complete, many examples of every disease process would be needed, for there is no such thing as a typical appearance. Mr A. P. Bertwistle, in the 7th edition of this well-known book, has made a fairly representative selection, but there are some inevitable gaps.

In his introduction he declares that his aim is to show the capabilities of *x* rays and in the main he succeeds in this, but one regrets the omission of any examples of angiocardiograms, the recent development of which would appear to be of increasing importance. Few heart conditions, indeed, are represented. One would also

like to see examples of lateral chest films demonstrating lobar and segmental lung lesions. The appearance in this edition of a section on helminthology is welcome, though the reproductions are not, perhaps, quite up to the standard of the rest of the work. One would have welcomed a general word on capabilities and limitations as an introduction to each section.

The book is well produced and pleasingly free of misprints. The *x*-ray reproductions are, however, positives; to some, this may be a disadvantage. Many of the plates are accompanied by useful line diagrams which greatly assist in interpretation.

The book includes a most interesting and informative chapter on the milestones in radiodiagnosis; however, a bibliography of the work referred to would have been a useful addition.

This atlas should prove of value to the practitioner who is taking an intelligent interest in the ever-expanding science of radiodiagnosis and also to the student, as a supplement to that study of radiology which can truly be accomplished only at the bedside.

F. D. Beddard

1566 Standard Radiographic Positions

Nancy Davies & Ursel Isenburg. Second edition. London: Baillière, Tindall & Cox, 1947. viii + 223 pages; 384 figures. 23 × 16 cm. £1 1s. [£1.05]

(i) Upper extremity; (ii) shoulder girdle; (iii) lower extremity; (iv) pelvic girdle; (v) spinal column; (vi) thoracic bones; (vii) skull; (viii) teeth; (ix) internal organs; (x) localisation of foreign bodies; (xi) stereoscopic radiography; (xii) the X-ray department; (xiii) the patient. Exposure chart. Index.

This book has been considerably enlarged since the 1st edition, and the radiographic data included have been brought up to modern standards. The section dealing with the skull, sinuses and mastoid positions is very ably written, and the diagrams are a useful reference for information about the various projections required by radiologists. The section on the preparation of the patient for various *x*-ray examinations is also very useful. Although preparation varies slightly in different departments the book is a good general guide to radiographers. For example, the section on bronchography includes a list of needles, dressings, forceps, etc., required during the examination. Other radiographic procedures are equally well described. The exposure chart section is concise and can be adapted to suit individual requirements on different types of *x*-ray apparatus.

This work will be an invaluable aid to student radiographers at the commencement of their training and the diagrams will be of assistance to them in anatomical drawing. It would be useful as a reference book in any *x*-ray department. The authors and publishers are to be congratulated on a good production, which has the added advantage of being reasonable in price.

L. Smith

SURGERY

1567 Operative Surgery

Frederick C. Hill. New York: Oxford University Press; London: Geoffrey Cumberlege, 1949. xii + 698 pages; 255 figures. 24 × 16 cm. £3 3s. [£3.15]

(i) Preoperative treatment; (ii) general considerations; (iii) sutures, ligatures, and instruments; (iv) the skin and subcutaneous tissue; (v) the mouth, tongue, and salivary glands; (vi) the neck; (vii) the mammary gland; (viii) the pleura and lung; (ix) the mediastinum and contents; (x) the abdominal wall; (xi) the peritoneum, retroperitoneal tissue, and adrenal gland; (xii) the liver; (xiii) the gallbladder and bile ducts; (xiv) the pancreas; (xv) the spleen; (xvi) the stomach; (xvii) the duodenum; (xviii) the jejunum and ileum; (xix) the appendix; (xx) the colon; (xxi) the rectum and anus; (xxii) the uterus, Fallopian tube, and ovary; (xxiii) the female external genital organs, perineum, and vagina; (xxiv) the kidney and ureter; (xxv) the bladder and prostate; (xxvi) the male external genital organs; (xxvii) the bones and joints; (xxviii) the blood vessels; (xxix) the extremities; (xxx) postoperative treatment. Index.

Professor Hill, Associate Professor of Surgery in the Creighton University School of Medicine, Omaha, Nebraska, has produced a textbook of operative surgery suitable for students, interns, and junior surgeons. For the coverage of operative surgery which it affords, the book is compact. Not only technical details of operations are described, but pre-operative and postoperative treatment are considered at some length, and the positioning of the patient on the table and the draping of the operation field are explained in fuller detail than in most textbooks; surgical pathology, also, is well described. General operative methods, such as the tying of knots and the insertion of stitches, together with the different uses of the common surgical instruments, are very simply and concisely handled. In general, the author advises for each condition one single technique which he himself has found suitable, and which in most cases is a standard operative procedure. A careful selection has been made of relatively common procedures, and out-of-the-way operations are not described at any length. Plastic surgery is considered fairly fully, and the section on chest surgery is just what the undergraduate student requires. In most of the chapters dealing with the anatomical regions, operations which have a purely historical interest have been wisely omitted; in the chapter on the stomach, however, this does not altogether apply. The Roux type of anastomosis is described, for example, as also is wedge resection of a gastric ulcer. Approximately one-tenth of the book is devoted to gynaecology.

Perhaps the strictest selection has been in relation to orthopaedics, but, occasionally, the operations chosen for description seem a little strange. The general management of amputations, for example, and the principles which govern amputations at given levels, are rather inadequately considered, while a method for the removal of the intervertebral disk is discussed in some detail. It is proper to say that the precise operative technique for amputations at the common levels is described.

The lay-out of the textbook is really excellent, the style is simple, and the book is easy to read. As a review of the field of operative surgery for the undergraduate student it can be very highly commended.

Ian Aird

1568 A Short Practice of Surgery. Parts I-V

Hamilton Bailey & R. J. McNeill Love. Eighth edition. London: H. K. Lewis & Co. Ltd., 1948–49. 1,050 pages; 1,198 figures. 22 × 14 cm. £2 12s. 6d. the set [£2.625]

Part I. (i) Non-specific infections and wounds; (ii) specific infectious diseases; (iii) tumours; (iv) ulceration and gangrene; (v) blood and blood-vessels; (vi) lymphatics and lymphatic nodes; (vii) face and jaws, including the palate; (viii) teeth and gums; (ix) mouth and tongue: floor of mouth; (x) salivary glands; (xi) neck; (xii) thyroid gland; (xiii) thymus, parathyroid, and adrenal glands. Index. Part II. (xiv) Pharynx; (xv) oesophagus; (xvi) peptic ulcer; (xvii) stomach and duodenum; (xviii) spleen; (xix) liver; (xx) gall bladder and bile ducts; (xxi) pancreas; (xxii) peritoneum; (xxiii) intestines; (xxiv) intestinal obstruction; (xxv) vermiform appendix. Index. Part III. (xxvi) Rectum and anal canal; (xxvii) hernia; (xxviii) urinary symptoms. Investigation of the urinary tract. Anuria; (xxix) kidneys and ureters; (xxx) urinary bladder; (xxxi) prostate and seminal vesicles; (xxxii) urethra and penis; (xxxiii) testes and scrotum; (xxxiv) skin. Index. Part IV. (xxxv) Head; (xxxvi) spine; (xxxvii) nerves; (xxxviii) special nerves; (xxxix) breast; (xl) thorax; (xli) larynx; (xlii) infections of the hand. Index. Part V. (xliii) Injuries to the bone; (xliv) diseases of bones; (xlv) injuries to joints; (xlvi) diseases of joints; (xlvii) muscles, tendons, and bursae; (xlviii) deformities. Glossary. Index.

It is difficult to know what to say about the re-appearance of so well-known a "Short Surgery" even though it is disguised in five volumes, all coloured differently; but the appearance of an 8th edition speaks adequately for its popularity and use. The authors state that they have presented the book in sections because of the delay between the written and the printed word enforced by economic conditions in Britain today. This reviewer feels, however, that the time-lag, regrettable as it is, is not long enough for the principles of surgery to alter materially, and it is certainly a disadvantage for reference purposes to have a book in small sections.

The authors and publishers are to be congratulated on a very neatly turned out and well-finished series of volumes, which are profusely illustrated, as indeed are all the works of these two authors. While one agrees with the Chinese proverb quoted in the preface: "One picture is worth a million words", one must point out that there is a limit to the reduction in size of that picture, below which it ceases to illustrate the point requiring emphasis. This criticism applies to more than one of the illustrations in this work,

and especially to those, otherwise excellent and valuable, illustrating Dr. Hermitte's admirable pathological disquisitions.

The technical material is well arranged in sections and is dealt with tersely but adequately. All superabundance of detail, both in clinical signs and in treatment, is skilfully avoided. This is as it should be in a work which is intended only as a book of reference for the practitioner and surgeon, and not as the sole textbook of the undergraduate student. The authors are to be congratulated again on having produced a concise and comprehensive work which is of great value as a refresher course and a reference book; and they can feel assured of the continued popularity of their efforts.

Philip H. Mitchiner

1569 An Atlas of Traumatic Surgery: Illustrated Histories of Wounds of the Extremities

Josep Trueta. Oxford: Blackwell Scientific Publications, 1949. viii + 150 pages; 188 figures. 25 × 19 cm. £1 10s. [£1.5]

Introduction. (i) Upper limb; (ii) lower limb.

Professor Trueta's work is, as it professes to be, an atlas of many photographs showing the progress and end-results of the author's well-known and oft-advocated treatment of all wounds by early and thorough excision of destroyed and damaged tissue, and as such it pays tribute to the success of his methods and the correctness of his views. He is perhaps inclined to assume that before the Spanish Civil War no thorough and far-reaching excisions with subsequent plaster of Paris immobilization had been undertaken, at any rate with success, in any prior war, but he may rest assured that such methods were practised, and with success, especially by the French military surgeons on the Salonika front in 1916–18. Professor Trueta correctly acknowledges the value of chemotherapy as an adjunct, but *only* as an adjunct, to the success of early root and branch excision of wounds, and rightly stresses that in the presence of chemotherapy delayed union in some eight to ten days should be the routine practice in securing the early closing of the majority of war wounds. The illustrations are well produced, but in some cases might be considered as failing to convey the points required to show the uninitiated surgeon (on Professor Trueta's own admission he is writing hopefully for the presumably uninitiated surgeon in a war in the dim future) the full and terrible destruction of tissues which he must expect to meet and the root and branch surgery which he must carry out promptly and adequately if success is to be attained by these methods.

Professor Trueta is to be congratulated on this work which, like all his previous publications, is clear, helpful and instructive.

Philip H. Mitchiner

1570 Demonstrations of Physical Signs in Clinical Surgery

Hamilton Bailey. Eleventh edition. Bristol: John Wright & Sons Ltd., 1949. xii + 426 pages; 657 illustrations. 23 × 14 cm. £1 14s. [£1.7]

(i) Introductory; (ii) some basic physical signs; (iii) some general principles in the examination of joints; (iv) localized swellings; (v) signs of local inflammation: ulcers and sinuses; (vi) the mouth; (vii) the salivary glands; (viii) the face and jaws; (ix) the head; (x) the ear; (xi) the neck (excluding the thyroid gland); (xii) the thyroid gland; (xiii) the breast and axillary lymph-nodes; (xiv) the thorax; (xv) the shoulder, arm, and forearm; (xvi) the hand: (xvii) hernia. Lymphatics of groin; (xviii) non-acute abdominal conditions; (xix) non-acute abdominal conditions—special demonstrations; (xx) rectal and vaginal examination; (xxi) clinical examination of the urinary organs; (xxii) the male generative organs; (xxiii) common acute abdominal conditions; (xxiv) abdominal and pelvic injuries; (xxv) some rarer acute abdominal conditions; (xxvi) the sacro-iliac joint; (xxvii) the hip-joint; (xxviii) the knee-joint; (xxix) the leg and foot; (xxx) bone; (xxxi) the spine; (xxxii) the peripheral nerves; (xxxiii) examination of the blood-vessels of the extremities: threatened and established gangrene; (xxxiv) some signs to confirm a suspicion of neurosis. Glossary. Index.

In welcoming this new, 11th edition of Hamilton Bailey's book, one is astonished to find that the 1st edition appeared no less than 23 years ago. One can still recall the immediate and powerful appeal which it made to the medical student and there is little doubt that this latest edition will hold a similar attraction for the students of the present day.

The reason for the initial and continued popularity of this book is not far to seek. The author set out to demonstrate physical signs and to describe clearly to the student how he could elicit these signs, an object which would inevitably meet with the approval of all medical students. If in any given case the student can obtain an accurate history and can carefully elicit and record the physical signs present, then he has the diagnosis ready-made, as it were. But if, on the other hand, unskilful examination has not only failed to elicit signs present but has discovered signs which in fact are not present, he will be misled by these false data and make a wrong diagnosis. It is, of course, the duty of the clinical teacher to demonstrate to his students how to elicit these signs, but it is a duty which one feels is at times neglected.

The two main methods available to the author, to enable him to fulfil his purpose, were careful descriptions of the methods of examinations, and good illustrations. The descriptions given in this book have always been excellent, clear and concise, but the great, and, at the time of its original publication, the novel virtue of the book was the lavish use of excellent illustrations, mostly first-class clinical photographs. It is perhaps not too much to say that this book when it originally appeared set up a new standard for medical textbooks in this respect.

These original virtues have never been allowed to fade. Indeed with each succeeding edition endeavour has been made to improve on its predecessor. Colour photography has been used increasingly, diagrams are excellent and the whole production reflects great credit on the author and his publishers. The continued popularity of the volume is assured by the issue of this new edition.

T. M. Millar

1571 A Text-Book of Surgical Pathology

Charles F. W. Illingworth & Bruce M. Dick. Sixth edition. London: J. & A. Churchill Ltd., 1949. viii + 726 pages; 317 illustrations. 24 × 16 cm. £2 5s. [£2.25]

(i) Inflammation; (ii) wound infections; (iii) constitutional effects of injury; (iv) tuberculosis; (v) actinomycosis; (vi) hydatid disease; (vii) tumours; (viii) diseases of bones; (ix) diseases of joints; (x) diseases of muscles, tendon sheaths and bursae; (xi) diseases of blood vessels; (xii) diseases of lymph glands and vessels; (xiii) diseases of the skull and brain; (xiv) diseases of the spine and spinal cord; (xv) diseases of peripheral nerves; (xvi) diseases of the thorax; (xvii) diseases of the pericardium, heart and great vessels; (xviii) diseases of the breast; (xix) diseases of the mouth, jaws, salivary glands and neck; (xx) diseases of the thyroid gland; (xxi) diseases of the parathyroid glands; (xxii) diseases of the pharynx, larynx and oesophagus; (xxiii) diseases of the stomach and duodenum; (xxiv) diseases of the small intestine; (xxv) diseases of the colon; (xxvi) diseases of the vermiform appendix; (xxvii) diseases of the peritoneum; (xxviii) diseases of the gall-bladder, liver and bile ducts; (xxix) diseases of the pancreas; (xxx) diseases of the spleen; (xxxi) diseases of adrenal glands; (xxxii) diseases of the urinary organs; (xxxiii) diseases of the male generative organs; (xxxiv) diseases of the female generative organs. Index.

The 1st edition of this textbook was published 18 years ago. In this, the 6th edition, there are new chapters on diseases of the heart and blood-vessels; and accounts of vascular hypertension, causalgia, and tumours of muscle have been added. The descriptions of thrombophlebitis, peptic ulcer, intestinal obstruction, and several other conditions have been re-written.

"This book has been written for graduates and senior students" and the authors have made "only passing reference . . . to such fundamental processes as inflammation, suppuration, ulceration and repair." These subjects are dealt with in the first chapter of 11 pages. The "passing references" are elementary and uninspiring and several opportunities are lost of stressing the importance of modern research in inflammation and trauma. Having the seniority of the reader in mind, there seems to be little point in retaining this rather inadequate first chapter, especially as these fundamental subjects are dealt with fully in most standard textbooks of general pathology.

The same criticism applies to the second chapter, dealing with wound infection. The account of the staphylococci occupies 15 lines. The surprisingly high proportion of normal individuals of all ages who carry pathogenic staphylococci in the nasal vestibule is not even mentioned. Staphylococcal coagulase is described as an exotoxin and no mention is made of the important practical value of distinguishing between pathogenic and non-pathogenic strains by testing for coagulase production. The account of the streptococci is brief and contains some inaccuracies. The description of the pathogenesis of gas gangrene is misleading, as no clear distinction is made between the growth requirements of clostridia, which are relatively unimportant, and the local and general lethal effects of specific clostridial toxins, which are fundamental. It is not improbable that students reading this book may be misled into thinking that these references to bacteriology contain all that a well-informed and intelligent surgeon can be expected to know. If this is a real danger, it might be considered advisable in future

editions to omit these " passing references " unless sufficient space can be found to deal with the subjects more fully.

The remainder of the book deals with the morbid anatomy and histology of diseases of surgical importance. It is quite clearly this part of the book which has ensured its popularity with students for the last 18 years. The chapters on the pathology of bone and peripheral vascular disease are outstanding and, of the re-written chapters, that on the spleen is excellent. The problem of fluid balance is given the prominence and careful explanation which it so fully deserves.

Geoffrey Hadfield

1572 Acute Injuries of the Head, their Diagnosis, Treatment, Complications and Sequels

G. F. Rowbotham. Third edition. Edinburgh: E. & S. Livingstone Ltd., 1949. xx + 480 pages; 259 figures. 25 × 18 cm. £1 15s. [£1.75]

(i) The mechanisms of injuries of the head; (ii) pathology; (iii) diagnosis of closed injuries of the head; (iv) treatment of closed injuries of the head and surgical technique; (v) fractures of the skull; (vi) open or compound wounds of the head; (vii) traumatic osteomyelitis; (viii) results of injury to special parts of the brain and skull; (ix) the sequels of injuries of the head; (x) rehabilitation; (xi) post-traumatic epilepsy; (xii) the final results of head injuries; (xiii) the mechanism of birth injuries; (xiv) the residual illness. Index of authors. General index.

Mr Rowbotham introduces the subject of acute injuries of the head with a comprehensive and scientific survey of the physical mechanisms by which the skull, the brain and its membranes may lose continuity. He describes and illustrates the pathology of acute head injury anatomically and statistically, and deals at length with the problems of concussion and of the conduct of air-raid casualties. Drawing upon his knowledge of surgical literature, of physics, and of his own experiences, he discusses the diagnosis of closed injuries of the head in terms of the difficulties raised by the complex picture of each head injury and freely gives his opinion on matters of controversy. Whilst his methods of treatment of closed head injuries are not universally accepted, he gives them very full descriptions, and states their indications; closed cranial fractures and defects are described and treated along the usual lines.

Dealing with compound wounds of the head and such complications as cerebrospinal rhinorrhoea, he shows how war experiences have contributed to the treatment of these injuries and how thorough the approach to traumatic osteomyelitis must be. The chapter on injury to special parts of the brain makes interesting reading and has very useful statistical references; with descriptions of the sequelae of head injuries, much space is devoted to the social, psychological and medicolegal aspects of both diagnosis and treatment, and rehabilitation is elaborated with realism. The difficult subject of post-traumatic epilepsy is carefully reviewed and the management of cases of late onset advised. After a short survey of some statistics of late results of head injury, and a summary of the mechanism, diagnosis and treatment of birth injuries, Mr Rowbotham concludes with a final note on the relation between the head injury, the original personality of the individual, and the type and circumstances of the work and society to which the individual returns.

Too controversial and *décousu* for the undergraduate, this book should be read by every resident surgical officer; let him not, however, be deterred by those passages which he cannot understand, for the author boldly attacks all controversial matters and the book is the result of his wide reading and surgical experiences in the field of traumatic craniocerebral surgery.

W. J. Atkinson

1573 Abdominal Operations

Rodney Maingot. Second edition. London: H. K. Lewis & Co. Ltd., 1948. xxiii + 1274 pages; 468 figures. 25 × 17 cm. £4 4s. [£4.2]

Part I. Abdominal incisions. Part II. Stomach and duodenum. Part III. Spleen. Part IV. Pancreas. Part V. Gall-bladder and bile ducts. Part VI. Liver. Part VII. The vermiform appendix. Part VIII. Peritoneum, mesentery, omentum. Part IX. External abdominal hernia. Part X. Intestines. Part XI. Post-operative chest complications: diaphragmatic hernia: portal hypertension. Index.

Maingot's *Abdominal operations* was published first in 1940 and quickly achieved recognition as an authoritative work. It covers more than its title indicates, for it is concerned not merely with the technique of operations, but with the whole care of the patient during his stay in hospital. Thus in the chapter on duodenal ulcer, after sections devoted to etiology, symptoms and diagnosis, there is a discussion on the choice of treatment, followed by a review of the principles of medical care, and finally a detailed account of the operations, with appropriate measures of preparation and after-care.

In this 2nd edition, Maingot has been assisted by several other surgeons. In addition to English colleagues they include Harold Dew of Sydney, who writes on hydatid disease; Lester Dragstedt on vagotomy; and Stuart Harrington on diaphragmatic hernia. Maingot himself, however, remains responsible for the greater part of the book, which thus avoids the unwieldiness and diversity of approach so often to be found in works of multiple authorship.

As is to be expected, the teaching throughout is entirely up to date, and the descriptions of operative technique are sufficiently detailed to be of real value to the surgeon. A special word of praise is deserved for the illustrations, which are excellent.

C. F. W. Illingworth

1574 Acute Intestinal Obstruction

Rodney Smith. With a chapter on radiological diagnosis, by *Eric Samuel.* London: Edward Arnold & Co., 1948. xii + 259 pages; 102 figures. 22 × 14 cm. 18s. [£0.9]

(i) The history of the surgery of acute intestinal obstruction. Pathology. (ii) General principles of pathology; (iii) simple occlusion; (iv) closed loop obstruction; (v) intestinal strangulation; (vi) functional intestinal obstruction; (vii) peritonitis and acute intestinal obstruction; (viii) protein deficiency in intestinal obstructions. Diagnosis. (ix) Clinical diagnosis; (x) radiography in acute intestinal obstruction. Treatment. (xi) The place of chemotherapy; (xii) the place of suction drainage; (xiii) the treatment of protein deficiency; (xiv) the relief of obstruction without operation: the conservative plan. Pre-operative treatment. (xv) The operation; (xvi) postoperative treatment. Individual varieties of acute intestinal obstruction. (xvii) Classifications; (xviii) congenital anomalies; (xix) strangulated external hernia; (xx) strangulated internal hernia; (xxi) obstruction by bands and adhesions; (xxii) volvulus; (xxiii) intussusception; (xxiv) acute obstruction by a neoplasm; (xxv) acute obstruction from inflammatory changes in the gut wall; (xxvi) intraluminal impaction; (xxvii) mesenteric vascular occlusions; (xxviii) functional intestinal obstructions; (xxix) postoperative intestinal obstruction. References. Index.

This practical monograph sets forth a modern account of the problems which present themselves in a case of suspected or confirmed intestinal obstruction. A thoughtful and encouraging foreword by Vaughan Hudson emphasizes the value of radiology in the detection of early obstruction, and pays tribute to former surgeons of the Middlesex Hospital who were pioneers in the diagnosis and treatment of these often difficult cases.

In his preface the author stresses the fact that the obstruction in itself is not immediately lethal, and that correction of dehydration and the adoption of intestinal suction are modern methods of treatment which will often tide the patient over the immediate crisis. The pathology of obstruction is then discussed, and the importance of protein deficiency and the correction of hypoproteinaemia by the oral or intravenous administration of amino-acids is emphasized. The section on diagnosis of acute obstruction is clear and concise, but the clinical examination of the abdomen surely merits more space than less than one page, especially as the chapter on radiography is allotted no less than 27 pages! Intraperitoneal chemotherapy is next considered, but no mention is made of microform suspension, which is the ideal preparation for combating peritoneal infections.

The treatment of various types of obstruction is considered in detail. A popular error is reiterated in connexion with a strangulated inguinal hernia, when it is stated that such a hernia is irreducible. The ideal treatment of a strangulated inguinal hernia of less than six hours' duration, provided it is previously reducible, is taxis, i.e., manual reduction. This is often accomplished by the patient himself, or by the medical attendant, and then the desirability of a subsequent operation can be considered at leisure.

It is also stated that, in the case of a strangulated inguinal hernia, abdominal examination reveals signs of early obstruction with hyperperistalsis. This statement may mislead the junior surgeon, as hyperperistalsis is absent in the case of Littré's hernia, or when omentum or a Fallopian tube is present in the sac.

Methods by which the viability of strangulated bowel is assessed are mentioned, but one important omission is the aid which can be given by the anaesthetist. In a doubtful case, the administration of pure oxygen for a period of two or three minutes is sometimes the deciding factor, as the colour of viable gut will then approximate to normal.

Mention is made of " prune juice " stools in acute intussusception. The stools in this condition are more correctly described as re-

sembling red currant jelly, as they are a mixture of mucus and blood. Physicians reserve the term "prune juice" to describe the expectoration which typifies a lung carcinoma. Vague and meaningless terms are not infrequent. How can a thoughtful reader assess such terms as "a fair number of recorded cases" or "a high percentage of cases"? The "baby boy" who is likely to suffer from an acute intussusception would better be described as a male infant of from six to nine months. What are the actual dimensions of the "large" gallstone which becomes impacted in the jejunum? It is generally accepted that a diameter of more than one inch will fail to negotiate the small intestine.

However, in spite of these defects, and other minor ones, which can be corrected in a subsequent edition, this book is a useful guide to a junior surgeon who is responsible for emergency work, and as such it can be warmly recommended.

R. J. McNeill Love

1575 Wounds of the Extremities

Edited by *H. J. Seddon*. Bristol: John Wright & Sons Ltd., 1949. (*British Journal of Surgery* War Surgery Supplement No. 2.) 104 pages; 75 figures. 26 × 18 cm. 12s. 6d. [£0.625]

(i) War injuries of the extremities and their treatment in forward areas; (ii) missile wounds involving bone; (iii) early treatment of penetrating wounds of joints; (iv) war injuries of peripheral nerves; (v) war injuries of the peripheral arteries.

The production, by the *British Journal of Surgery*, of a War Supplement which is devoted to wounds of the extremities, has admirably filled a gap in post-war surgical literature. In general presentation the supplement maintains the high standard of the first War Supplement of the *British Journal of Surgery*, which dealt with head injuries, and it contains many excellent illustrations, a valuable bibliography, and much useful statistical data. Under the able editorship of Mr H. J. Seddon, the subject is handled in five sections, and deals with treatment in forward areas, and the management of injuries involving bones, joints, peripheral nerves, and peripheral arteries.

There is no hint of smugness in these expositions; yet, throughout, the reader is aware of the very considerable progress made over the methods and results of the First World War. The Winnett-Orr technique, developed and extended in the Spanish Civil War, was thoroughly proven, and stood the test of the many varying conditions of the Second World War. The impact of chemotherapy, and in particular of penicillin, on the management of wounds is here well described. The initial enthusiasm for this method of treatment, with facile abandonment of surgical principles, was followed by the rapid realization that chemotherapy was but an aid to, rather than a substitute for, early and thorough surgical treatment. The better control of infection, together with early ambulation, more intensive rehabilitation, and the energetic use of such time-savers as early skin-grafting, all contributed to a greatly diminished period of hospitalization, and to a quicker return to full duty—the prime aim of a military surgeon. Vascular surgery benefited from segregation into special units, but the introduction of anticoagulants, which have so widened the possibilities of reconstructive arterial surgery, came too late to help in the management of war injuries.

It is a melancholy thought that all the valuable experience herein set down may be of little use to surgeons in a future conflict, in which wounds from missiles may seem very insignificant compared with new varieties of trauma from heat and radioactivity.

J. P. Bentley

1576 Ulcers and Eczema of the Leg: Sequels of Phlebitis, etc. Studies on Static Diseases of the Lower Limbs and their Treatment

Holger Bisgaard. Copenhagen: Einar Munksgaard, 1948. 111 pages; 36 figures. 25 × 16 cm. 15 Dan. kr.

Introduction. (i) Uncomplicated cases of infiltration; (ii) infiltrations and varicose veins; (iii) infiltrations and phlebitis; (iv) infiltrations and thrombophlebitis; (v) infiltrations and ulcers of the leg; (vi) infiltrations and eczema of the leg; (vii) infiltrations complicated by the deformity: "three star" cases; (viii) infiltrations complicated by the deformity crura quadrata; (ix) infiltrations and arthrosis deformans; (x) infiltrations in the most severe and last stage.

Dr Bisgaard's approach to the problems resulting from man's adoption of the erect posture was both stimulating and original. Until his recent death, Bisgaard worked as a general practitioner in Denmark, so that his methods of treatment of ulcers, eczema, and oedemas of the legs were basically empirical. They, nevertheless, proved so successful in practice that they came to be employed in the State Hospital in Copenhagen, and earned the praise and support of Professor Haxthausen himself.

Bisgaard's thesis is briefly this: that a great deal of disability from pain, swelling, heaviness, and fatigue in the distal part of the legs arises from filtration oedema. This oedema, which Bisgaard calls an infiltration, may have a central or peripheral cause, but is itself responsible for many crippling sequelae. Thus, whilst he acknowledges that varicose veins are a common cause of infiltration, he lists many other causes as common, such as anaemia, heart disease, postoperative debility, and pregnancy, and, locally, fractures and phlebitis. He goes on to assert that the infiltration often persists for a long time after the causative factor has itself disappeared. Thus infiltration, from being a symptom, may become a disease.

Infiltration is recognized principally by a painful and tender puffiness in the malleolo-calcaneal spaces, especially on the inner side, and what Bisgaard calls the pathognomonic symptom is local pain and restlessness at night, relieved by movement. Bisgaard's treatment is meticulously described; it aims at dispersing the infiltration in three ways, by massage, by elastic bandaging, and by mobilization. Progress is assessed by repeated measurements of diameter at three levels in the leg. The latter part of the book contains case reports of cases of simple and complicated infiltrations, showing the benefit derived in each by the application of Bisgaard's methods of treatment.

Most workers in this country will probably feel that perhaps too much emphasis has been placed by Bisgaard upon this secondary phenomenon of infiltration, and that, in almost every case, appropriate treatment of the causative lesion will itself lead to the disappearance of the infiltration. In those cases, of course, in which infiltration is present without any treatable primary cause, elastic support has usually been resorted to. It is most valuable, however, to have Bisgaard's detailed instructions on how best to apply elastic support, and also to learn of the reliance he has placed on an exact technique of massage.

J. P. Bentley

1577 Varicose Veins

R. Rowden Foote. London: Butterworth & Co. Ltd., 1949. xiv + 226 pages; 181 figures. 2 coloured plates. 25 × 17 cm. £1 12s. 6d. [£1.625]

(i) Some historical landmarks in the treatment of varicose veins; (ii) anatomy, physiology and pathology; (iii) incidence and aetiology of varices; (iv) the investigation of the patient with varicose veins; (v) treatment; (vi) varicose ulceration; (vii) thrombophlebitis and pulmonary embolism; (viii) anticoagulant therapy; (ix) the supportive and compression treatment in varicose conditions; (x) the varicose vein clinic and some useful prescriptions; (xi) the recent work in varicose veins. Appendix A. Index.

Mr Rowden Foote is to be heartily congratulated on the high quality of this book, the first dealing solely with varicose veins to be published in Great Britain. The author rightly stresses the immense importance of varicose veins and their complications, in the life and work of the community, and reminds us of the astounding fact that during the last war varicose veins constituted the largest single group of admissions to hospitals in the Emergency Medical Service, accounting for almost 10% of all cases! The book covers the whole subject most comprehensively, starting with a historical survey, and passing through the etiology and pathology to a consideration of the various methods of treatment in vogue today.

His own preference for most cases is for a high ligation flush with the femoral vein, coupled with the distal injection of a phenol-glycerin-glucose solution through a "nutmeg-grater" needle by means of which mechanical, as well as chemical, trauma is applied to the tunica intima. This technique is said to give almost universally excellent results, though the theoretical objection remains that sclerosants injected into the thigh pass immediately into the deep venous system, as shown by Boyd and others in phlebographic studies. It might therefore seem possible for deep femoral thrombosis to be at any rate an occasional complication of this method of treatment. It would indeed be illuminating, also, if histological proof were available that the technique definitely avoided the incidence of recanalization of the internal saphenous vein after months or years. This is a crucial point. Bull and Hiatt of Columbia University, New York, believe that *no* method of treatment will prevent recanalization of the vein, and they have, in consequence, reverted to the old technique of total extirpation of the vein, using the Mayo vein stripper. They argue that every other method leads

to recanalization, with a thick-walled rigid vein and damaged valves, which, though not varicose, nevertheless causes venous back-pressure on distal areas, with all its attendant ills.

The whole book is splendidly and copiously illustrated, mostly with actual photographs, and detailed advice is given on many useful manoeuvres, from the application of a supportive bandage to the still insufficiently practised empty vein technique for the injection of sclerosants. There is also a most useful section dealing with the problems of thrombophlebitis and embolism, and anticoagulant therapy.

Throughout the book the author has made a praiseworthy and successful attempt to present the views of others as well as his own on this very controversial subject. Whilst indicating at each stage his own preferences, supported by cogent reasons, he has avoided the tendency to bigotry and dogma which so often characterizes utterances of those who have concentrated their interests on a relatively narrow and circumscribed field. In general, this book can be highly recommended to both surgeons and general practitioners, and is likely to become the standard work on the subject for some time to come.

J. P. Bentley

1578 Modern Practice in Ophthalmology, 1949

Edited by H. B. Stallard. London : Butterworth & Co. Ltd., 1949. xx + 525 pages ; 231 illustrations ; 30 colour plates. 25 × 17 cm. £3 5s. [£3.25]

(i) Anatomy and physiology ; (ii) pathology ; (iii) medical ophthalmology ; (iv) methods of examination ; (v) ocular therapeutics ; (vi) diseases of the eyelids ; (vii) diseases of the lacrimal apparatus ; (viii) diseases of the conjunctiva ; (ix) diseases of the cornea and sclera ; (x) diseases of the uveal tract ; (xi) diseases of the retina ; (xii) diseases of the optic nerve ; (xiii) diseases of the vitreous body ; (xiv) diseases of the lens ; (xv) glaucoma ; (xvi) refractive errors ; (xvii) strabismus and heterophoria ; (xviii) injuries of the eye ; (xix) diseases of the orbit ; (xx) tropical ophthalmology ; (xxi) surgical operations on the eye, eyelids and orbit. Appendix : standards of vision for the Services, etc. Index.

This book is written for the general practitioner, with the aim of providing him with a practical outline of modern ophthalmic practice, so that he may be able to share with the specialist the responsibility of treatment of ophthalmic cases or to deal with them efficiently in the absence of specialist help. This difficult task has been undertaken by a team of specialists who may be said to have achieved the first purpose of the book but to have fallen short, in some respects, of the second.

The first five chapters deal with general topics—anatomy and physiology, pathology, medical ophthalmology, methods of examination and general therapeutics. These are for the most part excellent, covering wide fields concisely and clearly. Then follow chapters on diseases of each of the structures of the eye in turn. Those on the lids, the conjunctiva and the retina are instructive and straightforward. The others, one feels, fail as guides to the uninformed by not being sufficiently schematic and dogmatic. The chapter on the cornea, for example, though interesting and unusual in its approach, leaves one groping for the signs, symptoms and treatment of, say, a hypopyon ulcer. In the chapter on glaucoma also, though all the information is there, the clinical pictures are not sufficiently clearly defined and no sharp distinction is made between acute and chronic types. The chapter on refractive errors is most comprehensive and instructive and that on strabismus and heterophoria could hardly be better. There is also a useful short chapter on tropical ophthalmology. The final chapter on operations is well illustrated but hardly realistic in some respects. Illustrated details of emergency operations, rather than of such operations as conjunctivo-dacryocystostomy or recession of the inferior oblique, would be of value to the practitioner in remote districts. There is a useful appendix on visual standards required for various Services.

A chapter on ophthalmic symptoms in general would have been a valuable addition and one's general impression is that the book might have been given more of a " vade-mecum " character without losing in attractiveness.

A. Lister

1579 The Science and Art of Joint Manipulation. Vol. I. The Extremities

James Mennell. Second edition. London : J. & A. Churchill Ltd., 1949. xv + 215 pages ; 299 figures. 25 × 19 cm. £1 4s. [£1.2]

Part I. General considerations. (i) Introduction ; (ii) the joint lesion ; (iii) referred pain ; (iv) general rules for manipulation. Part II. The joints of the upper extremity. (v) The digital joints ; (vi) the metacarpal joints ; (vii) the wrist region ; (viii) the radio-ulnar joints ; (ix) the elbow ; (x) the shoulder joint ; (xi) the clavicular joints. Part III. The joints of the lower extremity. (xii) The digital joints ; (xiii) the metatarsal joints ; (xiv) the tarsal joints ; (xv) the ankle region ; (xvi) the knee region ; (xvii) the hip joint. Index.

Of the three standard works on manipulation by British authors, this is the most exhaustive. It comes from the pen of the doyen of physicians practising manipulation, and summarizes the results of many years' experience.

General considerations include subluxation and adhesion-formation at joints, together with the bearing of the shape of the articular surfaces on function. This aspect of applied anatomy runs through the whole volume and is admirably set out. Referred pain is considered next, with emphasis on the segmental distribution of symptoms arising from spinal lesions. The next chapter deals with the principles governing manipulation, but the indications for and against forcing movement might well have been set out in greater detail. Caution is wisely enjoined and the reader learns that the history, the amount of movement present at the joint, and the *x*-ray appearances must be considered; but this important section on the nature and evaluation of these and other clinical signs could well have been expanded further. The present-day tendency to rely too much on the radiograph and to neglect clinical signs is justly criticized.

The joints of the extremities are considered each in turn. The shape of the bony facets is correlated with the separate patterns of movement achieved voluntarily and passively. The influence of joint-contour on the manner of performing a manipulation always receives masterly exposition, and there are textual descriptions and illustrations of as many as ten or twenty different ways of manipulating one joint, so that not only is a full range obtained of those movements which can be carried out by active effort, but a number of movements not capable of voluntary performance are also achieved. The elbow is dealt with in unorthodox fashion. The chapter on the hip joint is wholly admirable.

This book provides a fund of information for the clinician experienced in the diagnosis and treatment of the disorders met with in manipulative practice. Whoever wishes to study dynamic articular anatomy in its relationship to the manner of manipulating joints will enjoy every page of this important work.

J. Cyriax

1580 Structure and Function as Seen in the Foot

Frederic Wood Jones. Second edition. London : Baillière, Tindall & Cox, 1949. viii + 333 pages ; 155 figures. 22 × 14 cm. £1 5s. [£1.25]

(i) Introductory, dealing with the study of the foot ; (ii) the principles of terminology ; (iii) the human foot in phylogeny ; (iv) the foot in ontogeny ; (v) digital formula ; (vi) metatarsal formula ; (vii) external characters ; (viii) the fascias ; (ix) the bones ; (x) the accessory bones ; (xi) the sesamoid bones ; (xii) the joints ; (xiii) the extrinsic muscles ; (xiv) the morphology of the extrinsic muscles ; (xv) the intrinsic muscles ; (xvi) the morphology of the intrinsic muscles ; (xvii) the actions of the muscles ; (xviii) the movements of adduction, abduction and opposition of digits ; (xix) the movements of flexion and extension of the toes ; (xx) tendons, tendon sheaths and bursae ; (xxi) the arches of the foot ; (xxii) the foot and the brain ; (xxiii) the sensory nerves ; (xxiv) the motor nerves ; (xxv) the vascular channels. Index.

Over a quarter of a century ago Professor Wood Jones produced a rather novel anatomical book entitled *Principles of anatomy as seen in the hand*, in which the detailed anatomy of the hand was used as a text for generalizations on anatomical principles. This book deservedly became very popular and the author has recently written a companion volume, *Structure and function as seen in the foot*, now in its 2nd edition, which follows the same lines and is equally fascinating to read, although in view of the earlier treatise general principles have been described in less detail, while the special principles displayed in the structure and function of the foot have received more attention. This is no dull academic textbook describing structures on conventional lines, but a living anatomy from which we may not only learn the form, position, variations, morphology and functions of bones, muscles, joints and so on, but also may come to see the why and how. As an example of the particular method of presentation we may take the chapter on the vascular channels where it is shown how these vary from animal to animal depending upon such factors as the torsion of the limbs and their usual posture in use.

It is a sad commentary on the many conferences which have been held on anatomical nomenclature that the author has found it necessary to include a chapter, " The principles of terminology ", in which he suggests the use of such terms as " pre-axial " and " post-axial " in place of the more usual medial and lateral, to avoid

ambiguity. Nevertheless he has been unable to avoid such clumsy expressions as " the fibular-sided head of the bicipital flexor hallucis brevis ".

The physical anthropologist will find much useful information and much of interest in the chapters on digital and metatarsal formulae, and on the external characters of the foot (see Chapters V, VI and VII).

In Chapters III and IV there is a good discussion of phylogeny and ontogeny in their relationship to the origin of the human characteristics of the foot. As is well known, Professor Wood Jones holds some original and rather unorthodox views on the evolution of man and he has used many features in the development and structure of the foot as support for his general theory that the human foot is derived from a primitive mammalian foot. This part of the work is highly controversial and will undoubtedly be provocative. The author is particularly critical of what he terms the " gorilloid theory " of the evolution of man. " Those who look upon Man as being derived from a " gorilloid " stock see human foot structures as being direct developments from those present in the Gorilla. Those who derive Man from an earlier stock, from which the giant apes also arose, see, in the Gorilla foot, an inception of some of those specialisations already achieved in Man ". But it is only fair to point out that two of the authors whom he particularly picks out for criticism (Morton, D. J., *The human foot*; Lake, N., *The foot*) use the resemblances between the feet of gorilla and man precisely in this latter sense, i.e., as indicating the structural changes at the inception of the adaptation of the foot for bipedal progression; indeed, the author confesses that Morton's description of the forerunner of man as a relatively small-sized active and agile animal of erect posture is so unlike a gorilla that the term " gorilloid " would seem wrongly bestowed. Evidently the use of the word " gorilloid " is the " nigger in the wood pile ". Nevertheless it is proper to take a very broad view and to remember that apart from the foot there are other close resemblances between man and the large anthropoids which cannot be overlooked, such as blood-groups, precipitin reactions, and menstrual cycles, which seem to indicate that our relationship is a very close one indeed. The two opposing schools of thought approach the matter from opposite view-points, the one emphasizing the resemblances, the other the differences; this book records the latter attitude.

In dealing with ontogeny the author, correctly, in our view, states that the recapitulation theory is no more than a useful guiding principle and that it has largely lost its reputation for infallibility. However, if this is so, we can scarcely pay much attention to the statement that the internal cuneiform even in its earliest developmental stages shows no gorilloid characteristics in the distal joint surface, so that " be ancestral history what it may, it cannot be claimed that there is any embryological evidence that the ancestral human hallux was opposable, though it was doubtless divergent "; this would seem to involve the direct application of the recapitulation theory to a very small detail, and that, as the author himself says earlier, would " reduce this so-called law to absurdity ".

The comparative anatomy of the musculature of the foot is very well done but it is doubtful whether the writer's list of " features in which the muscles of the human foot show a plan more primitive than that existing in any monkey " would be accepted by some competent comparative anatomists.

Perhaps the most satisfactory summing up of the present position is by W. Straus: "In its musculature as in its skeleton and outer form the foot of the gorilla more closely approaches that of man than does the foot of any other primate. But at the present time it is difficult to decide which of these similarities are indications of close genetic relationships and which are merely due to convergence produced by interaction of environmental forces and an ancient ground plan ".

The question of the development of the arches of the foot is a very controversial one and it is interesting to record that Wood Jones does not entirely subscribe to the modern orthopaedic teaching that the arches are transient postural structures; he reinstates the ligaments in their important function of controlling the general form of the arch which itself is nevertheless " plastic and mobile " and capable of depression by body-weight and elevation by muscle action. This is a middle position between the extreme schools of thought on the subject and is probably correct.

Except for one or two small points the 2nd edition of this work is the same as the 1st. The book is full of interest and provocation; it is truly educative and stimulating and for these reasons can be highly recommended. There are a large number of line drawings by the author himself; their anatomical accuracy is thus assured and they clearly illustrate the arguments of the text.

Norman C. Lake

OBSTETRICS AND GYNAECOLOGY

1581 A Synopsis of Obstetrics and Gynaecology

Aleck W. Bourne. Tenth edition. Bristol: John Wright & Sons Ltd., 1949. vii + 522 pages; 167 illustrations. 19 × 13 cm. £1 1s. [£1.05]

Part I. A synopsis of obstetrics. Section I. Normal pregnancy. (i) The ovum, fertilization, and early development; (ii) chorion, amnion, placenta, umbilical cord, and foetus; (iii) changes in the maternal organism; (iv) diagnosis of pregnancy; (v) duration and management of pregnancy. Ante-natal care and examination. Section II. Abnormal pregnancy. (vi) Auto-intoxications; (vii) abnormalities of the generative tract; (viii) diseases of the ovum; (ix) ectopic gestation; (x) abortion; (xi) associated disorders. Section III. Normal labour. (xii) Physiology and course of labour; (xiii) mechanism of normal labour; (xiv) management of normal labour. Section IV. Abnormal labour. (xv) Occipito-posterior positions; (xvi) face and brow presentations; (xvii) pelvic presentations; (xviii) transverse positions; (xix) prolapse of cord and limbs. Twins; (xx) contracted pelvis; (xxi) difficult labour due to abnormalities of soft parts; (xxii) anomalies of uterine action; (xxiii) maternal injuries; (xxiv) ante-partum haemorrhage; (xxv) post-partum haemorrhage. Section V. The puerperium and the new-born child. (xxvi) Physiology and management of puerperal state; (xxvii) puerperal infection; (xxviii) sudden death and miscellaneous disorders in the puerperium; (xxix) the new-born child; (xxx) post-natal examination and care. Section VI. Obstetric surgery. (xxxi) Forceps; (xxxii) version; (xxxiii) induction of labour and abortion; (xxxiv) craniotomy—cleidotomy—evisceration—decapitation; (xxxv) caesarean section—symphysiotomy—pubiotomy. Part II. A synopsis of gynaecology. (xxxvi) Anatomy; (xxxvii) development and malformations of the genital organs; (xxxviii) sex hormones—menstruation—puberty—the menopause; (xxxix) amenorrhoea — menorrhagia — metrorrhagia; (xl) dysmenorrhoea; (xli) leucorrhoea; (xlii) infections of vulva and vagina; (xliii) infections of cervix and corpus uteri; (xliv) infections of Fallopian tubes, ovaries and pelvic peritoneum; (xlv) gonorrhoea; (xlvi) new growths and miscellaneous affections of the vulva; (xlvii) new growths, cysts, and fistulae of the vagina; (xlviii) fibromyomata; (xlix) malignant disease of the uterus; (l) ovarian and parovarian tumours; (li) displacements of the uterus; (lii) vaginismus, dyspareunia, and sterility; (liii) disorders of micturition. Index.

A specialist may be tempted to turn up his nose at a "synopsis" in his own subject. Any such tendency on the part of this reviewer was counteracted by the recollection of how he himself had often had hurried but beneficial recourse to a well-known synopsis of medicine, and by the thought that a synopsis of obstetrics and gynaecology could not be in better hands than those of a man of such proved independence of thought and judgement as Mr Bourne. He had to read no further than the preface to get confirmation of his view in the refreshing statement that the author had tried to suppress "out-dated ideas and methods, though the 'fixing' of teaching by the demands of examiners has prevented the deletion of some matter which has little relation to modern theory and practice."

In reviewing this little volume one has to keep ever in mind the narrow and irksome limits within which the author has had to work; and the same applies to the thumb-nail type of illustration which seems to be all that is admissible within the limits of a synopsis. Nor may the peculiar needs of the prospective readers be overlooked. It is not hard to detect some of the dead wood which Mr Bourne rightly regards as dear to the hearts of some examiners; and while the eradication of it from the synopsis would not uproot it from their minds, yet its retention here, as in any other widely-read book, merely tends to give its roots stronger attachment.

In view of the author's difficulties and of the fact that this is clearly not the type of book in which to stress individual views, we refrain from any detailed comment, but we must admire the masterly way in which the great mass of material has been handled. If one may parody Goldsmith's familiar couplet on the village schoolmaster, still the wonder grows how one small book can carry such a vast content of information.

The book is intended for rapid revisal of the subject by the student examinee, or for quick consultation on individual points by the busy practitioner. In both capacities it may be commended as a thoroughly reliable guide.

R. W. Johnstone

1582 The Anatomy of the Female Pelvis

F. A. Maguire. Fourth edition. London: Angus & Robertson, 1949. xv + 176 pages; 55 figures. 23 × 15 cm. £2 2s. [£2.1]

(i) The pelvic wall; (ii) muscles of the pelvis; (iii) pelvic fascia; (iv) the urogenital diaphragm; (v) the vulva; (vi) the pelvic viscera in general; (vii) the pelvic peritoneum; (viii) the pelvic connective tissue; (ix) pelvic blood-vessels and lymphatics; (x) the supports of the uterus; (xi) the uterus; (xii) the uterine (Fallopian) tubes; (xiii) the ovaries; (xiv) the vagina; (xv) the genital organs before, during, and after the reproductive epoch of life; (xvi) the structures between the layers of the broad ligament; (xvii) the lower urinary passages; (xviii) the lower bowel; (xix) the ischio-rectal fossa; (xx) applied anatomy; (xxi) the physical examination. Index.

It is close upon a decade since the previous edition of this little book was issued (the author being, in the interval, on active service) and it may not be as familiar as it deserves to be amongst present-day students.

Dr Maguire has the double qualification for writing such a book in that before advancing into gynaecology he was for six years the Professor of Anatomy in the University of Sydney. Perusal reveals a third qualification of no less importance—that he is obviously a man with a natural aptitude for teaching. Consequently his book offers a singularly clear and comprehensive account of its subject, with what one may call "teaching points" skilfully emphasized, particularly those with any special bearing upon either the design or the performance of gynaecological operations. It is, therefore, a book that should be most helpful to students of all grades of seniority who are preparing for examination in anatomy or in gynaecology, and not less so to those engaged in gynaecological operating or teaching. One of the best chapters is the last—on the physical examination of the pelvis in the living subject—where the clinical and scientific experience of the author is gathered up and blended in simple, clear instructions.

Sir William Fletcher Shaw has contributed a foreword in which he traces the evolution of those plastic operations on the female pelvic floor which form such a distinctive feature of modern gynaecology and for which we owe so great a debt to British gynaecologists and to the Manchester School in particular.

With 55 illustrations, semi-diagrammatic certainly, but beautifully drawn and admirably reproduced on art paper, this must have been an expensive book to produce, and both author and publishers are to be congratulated. One can only hope that medical students of today are more affluent than they were when an appreciative reviewer had the pleasure of being one of their number.

R. W. Johnstone

1583 Atlas of Mahfouz's Obstetric and Gynaecological Museum. Volume I

Naguib Pacha Mahfouz. Altrincham: John Sherratt & Son, 1949. xviii + 417 pages; 219 figures. 25 × 19 cm. £9 9s. the set of 3 volumes [£9.45]

(i) Structure of the genital organs: malformations of the female genital organs; (ii) the supporting structures of the genital organs: prolapse of the pelvic organs; (iii) menstruation and its functional disturbance; (iv) the pituitary gland during pregnancy; (v) the formation of the placenta: diseases of the membranes and placenta; (vi) disorders of pregnancy; (vii) hydatidiform degeneration of chorion: chorion-epithelioma; (viii) antepartum haemorrhage; (ix) the toxaemias of pregnancy; (x) the accidents of labour.

Few men can have had a richer experience or a more fruitful territory from which to derive a vast collection of pathological material than Mahfouz Pacha. Not only has he collected a unique museum of obstetrical, gynaecological and neonatal pathology, but his friends and colleagues have all lent a hand in swelling the total. There can be no museum in Britain which approaches this one.

It is therefore right and timely that a catalogue and atlas of his specimens should be published, and this very considerable work will appear in three volumes, the first of which is now available to the public. The production of this atlas must have given the author an immense amount of labour, for the book has obviously been compiled with meticulous attention to detail.

The author's plan has been to subdivide his subject into chapters, each of which starts with a short introduction. Although this is short, it is extremely succinct and contains more meat in a few lines than many a textbook in several pages. Mahfouz has rigorously excluded anything that is experimental, hypothetical and untried, and has steadfastly kept to the orthodox. In this way he may perhaps be criticized in certain places for being a little old-fashioned, but I think that, on the whole, this is a good trait in a book which will have a wide appeal to students. After the preamble there follows the series of illustrations in black and white, and in colour, relevant to the subject under discussion, each with a small sub-title in seven languages—French, German, Italian, Spanish, English, Arabic and Russian. These illustrations are superbly reproduced and the artist is to be congratulated. The histology is well reproduced.

It is difficult to pick out the best chapters in a book of a standard so uniformly good, but the chapters on the uterus and on hydatidiform mole and chorionepithelioma are outstanding. In fact, the latter is the best I can remember even in a textbook of gynaecology; and Mahfouz's *Atlas* is not a textbook.

There are few criticisms to be made about this book, but one or two points should be noted. First, there is a number of unfortunate spelling mistakes; the author should have his proofs read for the next edition by a classical scholar. It would also be an improvement to the next edition to have the names of those authors who are mentioned in the text tabulated for reference at the end of the chapter, so that the more advanced student would be able to explore the subject further should he wish to do so. This reviewer thinks it is a pity that a book which is going to have a wide appeal to the less opulent medical student should not be sold in separate volumes at 3 guineas each; to subscribe nine guineas for three volumes, two of which may not be delivered for several months, will deter a number of would-be purchasers.

Finally, every medical library and every medical school in the world should certainly have a copy of this *Atlas*. It will be of equal interest to teacher, specialist and student of the humblest qualifying examination. It bears the stamp of genius and is a monument to the unique experience of a man who has had one of the biggest gynaecological practices in the world.

J. Howkins

1584 Lehrbuch der Gynäkologie

Edited by *Hans Guggisberg*. Second edition. Basle: S. Karger, 1947. xiii + 717 pages; 354 illustrations. 25 × 17 cm. 72 Sw. fr.

(i) Anatomie des weiblichen Genitalapparates und seiner Nachbarorgane; (ii) die Entwicklung des weiblichen Urogenitalapparates; (iii) die Entwicklungsstörungen der Geschlechtsorgane; (iv) die Konstitution der Frau; (v) Konstitutions- und Wachstumsstörungen; (vi) die Physiologie der Frau; (vii) die Funktionsstörungen und die krankhaften Erscheinung des weiblichen Genitale; (viii) Pathogenese der organischen und funktionellen Genitalleiden; (ix) die gynäkologische Diagnostik; (x) die Erkrankungen des äussern weiblichen Genitale; (xi) die Erkrankungen der Vagina; (xii) die Erkrankungen des Uterus; (xiii) die Krankheiten der Ovarien; (xiv) die Erkrankungen der Tube; (xv) die Erkrankungen des Beckenbindegewebes und des Bauchfells; (xvi) die Erkrankungen der Bauchdecken; (xvii) die Erkrankungen des Darmes und ihre Beziehungen zum weiblichen Genitale; (xviii) die Erkrankungen der Harnorgane; (xix) die Infektion der Genitalorgane; (xx) Lage- und Gestaltveränderungen der Genitalorgane; (xxi) die Endometriosen; (xxii) die Sterilität; (xxiii) die Kontrazeption; (xxiv) die Therapie mit körpereigenen Wirkstoffen; (xxv) die physikalische Therapie; (xxvi) die Strahlentherapie; (xxvii) Diätetik (die therapeutische Verwendung der Vitamine); (xxviii) Hygiene der Frau. Sachregister.

Lehrbuch der Geburtshilfe. Vols. I and II

Edited by *Th. Koller*. Basle: S. Karger, 1948. xxiv + 1323 pages; 711 figures. 25 × 17 cm. 110 Sw. fr. the set of two volumes

Vol. I. (i) Geschichtlicher Überblick über die Entwicklung der Geburtshilfe; (ii) Embryologie des Menschen und Morphologie des Neugeborenen; (iii) die normale Schwangerschaft inklusive Schwangerschaftshygiene und Schwangerenfürsorge; (iv) die normale Geburt; (v) das physiologische Wochenbett (Puerperium); (vi) Physiologie des Neugeborenen; (vii) Mehrlingsschwangerschaft und Geburt; (viii) die Geburt aus Beckenendlage; (ix) die Pathologie der Schwangerschaft; (x) die Extrauteringravidität. Vol. II. (xi) Die regelwidrige Geburt; (xii) das pathologische Wochenbett; (xiii) die Missbildungen des Feten; (xiv) Pathologie des Neugeborenen. Sachregister.

This three-volume work comprehensively describes present-day Swiss teaching in obstetrics and gynaecology. The editors felt that such a work was more than ever necessary because of the non-appearance of German-language textbooks in these fields due to the recent war. The fact that a 2nd edition of vol. I was required within a few months of the publication of the 1st indicates the soundness of this judgement.

The first section of vol. I, *Lehrbuch der Gynäkologie*, deals with the anatomy of the female reproductive organs and is profusely illustrated. Unfortunately, many of these illustrations lack clarity, and perhaps might have been differently chosen with advantage. For example, the relationship between the ureter and the uterine artery is described in the text, but is not illustrated. There follow chapters dealing with the embryology and physiology of the female sex organs. Functional abnormalities are well documented and the medical, surgical and radiological treatment of these is fully considered.

The chapter on gynaecological diagnosis is up to date and present-day methods are fully described. The chapter on the pathology of the external genitalia is noteworthy because of its excellent coloured drawings, a contrast to the illustrations which appear earlier in the book. Noteworthy also is the fullness of treatment of myomata of the uterus.

Two volumes are devoted to obstetrics, titled vols. I and II, though listed as vols. II and III in the series. The chapters on normal pregnancy and labour are fairly full, though perhaps more stress might have been laid on the value and routine of antenatal care. The sections on the diseases of pregnancy and the pathology of labour and the puerperium are comprehensive and include a chapter on the pathology of the breast.

This work has been written by authors of great experience; it is perhaps a little too full for the undergraduate student, but will prove a trustworthy and valuable help to the postgraduate student and a useful reference volume to the specialist.

Oskar Burger

NEUROLOGY AND PSYCHIATRY

1585 International Congress on Mental Health, London 1948, Vols. 1, 2, 3 & 4

Edited by *J. C. Flugel*. London: H. K. Lewis & Co. Ltd.; New York: Columbia University Press [1949]. Vol. I: History, development and organisation. 154 pages; illustrations. 22 × 15 cm. 10s. [£0.5]. Vol. II: Proceedings of the International Conference on Child Psychiatry, 11th–14th August. xiii + 142 pages. 22 × 15 cm. 10s. [£0.5]. Vol. III: Proceedings of the International Conference on Medical Psychotherapy, 11th–14th August. xv + 129 pages. 22 × 15 cm. 10s. [£0.5]. Vol. IV: Proceedings of the International Conference on Mental Hygiene, 16th–21st August. ix + 330 pages. 22 × 15 cm. £1

Vol. I: (i) Origins and aims of the Congress; (ii) development of the programme; (iii) group work before and during the Congress; (iv) United States participation; (v) the International Preparatory Commission; (vi) press and publicity; (vii) organisation. Vol. II: (i) Aggression in relation to emotional development, normal and pathological; (ii) aggression in relation to family life; (iii) psychiatric problems in the educational sphere; (iv) the community and the aggressive child. Vol. III: (i) The genesis of guilt; (ii) guilt and dynamics of psychological disorder in the individual; (iii) collective guilt; (iv) advances in group and individual therapy. Vol. IV: (i) Problems of world citizenship and good group relations; (ii) the individual and society; (iii) family problems and psychological disturbance; (iv) mental health in industry and industrial relations; (v) planning for mental health: organisation, training, propaganda; (vi) conclusions and recommendations.

The 1948 International Congress on Mental Health, held in London under the presidency of Dr J. R. Rees, was not only one of the largest gatherings of its kind, but was conceived as an experiment in trans-national and inter-disciplinary communication. The first volume of its Proceedings deals with the steps taken to secure this end, and with the analysis of mistakes for those who come after. In this, the writers are perhaps hard on themselves as planners of the Congress. The feat of arousing some 4,000 persons, in many instances leaders in the field, from 28 different professions in 20 countries, to serious preparatory group discussions, fact-finding and even original research, some 18 months before the actual Congress, is probably unprecedented, and possibly the most significant among the achievements of this gathering.

In order to appreciate the material in the other three volumes it is essential to keep in mind that the Congress aimed less at individual brilliance than at finding the areas of agreement and disagreement among the disciplines concerned with promoting the purposes of a good society. Hearing and re-reading the statements from eminent psychiatrists, psychologists, social scientists and so forth, one is astonished at the rapidity with which their concepts, and even their language, have converged in the last decade. The cross-fertilization between disciplines, resulting from preparatory groups and from the efforts of individuals who had achieved considerable integration of psychological and sociological thinking, is evidenced in many papers and less formal contributions. Psychiatrists have begun to think socially and social scientists psychiatrically. A new science of "human relations" or "sociatry" is being born.

The Congress was a fusion of three conferences: on child psychiatry, on medical psychotherapy, and on mental hygiene, separately sponsored. Thanks to co-ordination, the major topics of each fitted into the theme of the whole: "Mental health and world citizenship". It is permissible to paraphrase the handling of this large subject by the Congress as "The study, diagnosis, therapy and prevention of the development of unhealthy or dangerous tensions within individuals, between individuals, within groups and between groups". Nearly half the published material consists of reports of the views of representative groups concerning such matters as aggression, guilt and their bearing on human relations. Among these expressions of common purpose and doctrine there are stimulating and profound discourses by distinguished leaders in the fields of psychiatry and social science. Margaret Mead, Franz Alexander, William Line, L. K. Frank, Anna Freud, T. F. Rodger and J. C. Flugel seem to stand out in this galaxy. The contents of these volumes, therefore, not only deal with recent work but are also authoritative and will repay careful study by any worker, whether concerned with individual welfare or with public hygiene, administration or policy.

This is perhaps especially the case with a succinct statement of basic concepts and practical recommendations for prophylactic action, prepared by a small, picked group of persons representing various countries and disciplines meeting for some weeks before the Congress—the so-called International Preparatory Commission (Vol. IV, p. 285 *et seq.*). The statement is a condensed but readable digest of current views and trends on a canvas sufficiently broad to be applicable to countries at all stages of mental health service development. Recommendations are grouped under the headings of "Principles underlying the practice of mental health", "Planning and organisation of national mental health services", "Education of the general public", "Education of specialists" and "Research". Recommendations for international action are addressed to the United Nations, the World Health Organization, and other specialized agencies. This statement was adopted with virtual unanimity by the Congress as a whole.

The main conclusions point to an acceptance of human nature as plastic, dynamic and capable of exhibiting an infinity of behaviour patterns; it is therefore capable of change and not predetermined. It is social habit or institution that is resistant to change. This offers a message of reasonable hope in our power to influence changes in such patterns by social, medical and educational action. The recommendations show that neither psychiatry, nor any other single discipline, has any illusions or grandiose fantasies about its powers to heal a distracted world. What emerges is a sober design for constructive assistance; mental health workers must broaden their conception of their work to include the total human situation rather than wait for patients to flood their clinics. The statement is a challenge to social policy. The front line of the battle for mental health lies in the education of parents, teachers, public health and infant welfare workers, and above all of policy makers and leaders of men, in the understanding of human beings, as individuals and in their social units, as ascertained by adequate scientific study.

The work accomplished by the Congress bids fair to cut the last bit of ground from under those who would still wish to maintain that the human sciences are nothing but warring camps and that medicine or classical economics can afford to ignore their teaching and their claim to contribute to human welfare. It is made clear that the World Health Organization and UNESCO have both officially signified their acceptance of the Congress recommendations and have conferred recognition on the World Federation of Mental Health founded during the Congress. One wishes these proceedings could be made obligatory reading in all postgraduate schools of medicine and of social science. The volumes are adequately produced and edited.

H. V. Dicks

1586 The Trend of Scottish Intelligence. A Comparison of the 1947 and 1932 Surveys of the Intelligence of Eleven-Year-Old Pupils

Sponsored by the *Population Investigation Committee* & the *Scottish Council for Research in Education*. London: University of London Press Ltd., 1949. xxviii + 151 pages; 7 figures. 22 × 14 cm. 7s. 6d. [£0.375]

(i) Introduction; (ii) administrative arrangements; (iii) sociological inquiry; (iv) individual testing; (v) correction of scripts and coding of sociological schedules; (vi) results of group test; (vii) intelligence and family size; (viii) comparison of the 1947 and 1932 individual test results; (ix) the implications of the 1947 survey.

At the beginning of the present century, fears were repeatedly expressed lest the alleged differences in fertility between the different social classes might not be producing a decline in the national intelligence.[1] The first actual surveys of intelligence, carried out by means of standardized tests, were those commenced in 1913 by Burt as Psychologist to the London County Council schools. The results revealed a small but undeniable negative correlation between children's intelligence and the size of the families from which they came. It was also shown that the correlation within each social class was quite as marked as the correlation with class differences; in fact, class differences as such proved a somewhat irrelevant factor.

[1] See also *Brit. med. Bull.* 1947, Vol. 5, pages 226 & 228.—ED.

The decline in average intelligence suggested by the figures was too small to be distinctly observable over a short period of time, particularly in an area like London with its shifting population. On the other hand, if no other factors were operative, the changes at the extreme ends of the scale, in the number of defectives and of scholarship children respectively, ought to have been discernible in the course of 10 or 20 years. But neither subsequent surveys nor the observations of teachers, school medical officers, or scholarship examiners, revealed anything like the increase in the changes deduced from arm-chair calculations. The conclusion tentatively suggested was that, partly but not wholly, the effects of differential fertility were being counterbalanced by the concurrent effects of certain genetic influences, easy to suggest but hard to prove.

This left the problem still undecided. Later investigations, like that of Dr Fraser Roberts at Bath, fully confirmed the negative correlation. And in 1932 a survey of all the children in Scotland born in 1921 was organized by the Scottish Council for Research in Education. No records were obtained at the time for the size of the various families. But in 1945 the Population Investigation Committee suggested a repetition of the survey, and undertook to secure the necessary financial aid. The suggestion was carried out in 1947; and the methods used and the data collected are fully described in the report now published.

The general arrangements were the same as before. An entire age-group, consisting of all the children in Scotland aged 11, was tested; and the same group test as that used in the 1932 survey was employed. So far from any decline being manifested, the average score turned out to be higher. The difference amounted to 2.3 points (somewhat more on an I.Q. scale), and was fully significant. The application of the individual tests to selected samples revealed a similar difference; but this might be explicable by a change in the Binet scale employed.

The main results have evidently come as a surprise to the investigators. They discuss various explanations that might account for the increase, and, on the whole, seem disposed to conclude that it is mainly due to increasing familiarity with intelligence tests of the type employed. So far, therefore, the main issue still remains unsolved. Further analyses of the data collected may conceivably lead to a more decisive conclusion. Meanwhile, the account of the planning, of the administrative organization, of the selection of tests, questionnaire items, and the like, will furnish much valuable assistance to those who may be contemplating similar surveys in the near future.

1587 Psychological Aspects of Clinical Medicine

Stephen Barton Hall. London: H. K. Lewis & Co. Ltd., 1949. xi + 416 pages. 22 × 14 cm. £1 1s. [£1.05]

(i) Introduction; (ii) investigation; (iii) intellectual development: psychometry and its application to medicine; (iv) emotional development and psychopathology; (v) common forms of psychoneurosis; (vi) psychological symptoms and physical disease; (vii) psychosomatic relationships; (viii) abnormal behaviour as a symptom of disease; (ix) relation of psychoneurosis to psychosis; (x) personality disorders; (xi) psychological aspects of management and treatment. Index of names. Index of subjects.

New books on psychiatry are plentiful, but many of them merely reflect the views of well-established works and are inferior to the originals. This book, however, is fairly new in concept and extremely ably written. The author has a sound grasp of his subject, and what he has to say is derived not merely from other books but from a wide clinical experience. His book covers those aspects of psychiatry which are likely to be of most concern to general practitioners and physicians; he develops his themes so steadily that his description of neurosis and psychosomatic relationships is reasonably easy to follow.

A minor criticism is that the chapter on psychopathology is somewhat condensed; the beginner would welcome more detail about mental mechanisms. Certain other criticisms on matters of detail could be made; for example, on page 59, dealing with the five grades of score on the progressive matrices tests, it is stated that grade 1 begins at the 95 percentile score; the other precentile scores given are also not those generally accepted. Grade 1 is usually placed at the 90 percentile score, grade 2 at the 70 precentile score, and so on. Again, on page 71 there is a numerical error. The sum of three weighted scores is multiplied by 5 and divided by 3, not multiplied by 5.3 as the text reads.

The conditions given on page 140 for the diagnosis of psychogenic illness compose an excellent summary which is well worth teaching to students as it stands. The list of physical conditions frequently diagnosed as functional in nature is an interesting, but a personal, one. In the opinion of this reviewer, disseminated sclerosis is diagnosed as functional more frequently than the author suggests; and visceroptosis must be regarded with some suspicion as an organic diagnosis.

In the discussion of psychosomatic disorders an important fact, which is indeed frequently overlooked, is omitted. It is usually stressed and is now well recognized that certain disorders may be neurotically determined; but surely the author must have seen many psychosomatic disorders which were secondary to psychosis? Asthma often occurs in agitated depression, and pruritus ani and vulvae are also seen as depressive symptoms. In the discussion on delirium in relation to infective illness, the fact that there is usually a diurnal variation might have been emphasized; it might also have been pointed out that the infective element is often missed and is by no means necessarily obvious.

The chapter dealing with the relation of the psychoneuroses to psychosis is extremely good, and the discussion of the differential diagnosis is sound. There is no doubt that there is a difference between severe exogenous depression and melancholia. In extreme degrees these conditions are obviously different, and in the reviewer's opinion are different at the beginning even in their milder forms. The author rightly stresses that psychoanalytic treatment of an early psychosis may be disastrous. In this, as in all branches of medicine, correct diagnosis is essential before commencing treatment.

The criticisms of this book are, after all, minor; it can be heartily recommended to medical students and physicians, and psychiatrists will also find it worthy of their attention.

Robert Orton

1588 An Introduction to Physical Methods of Treatment in Psychiatry

William Sargant & Eliot Slater. With a chapter on treatment of the epilepsies, by *Denis Hill.* Second edition. Edinburgh: E. & S. Livingstone Ltd., 1948. xv + 215 pages. 22 × 14 cm. 10s. 6d. [£0.525]

(i) The insulin treatment of schizophrenia; (ii) modified insulin therapy; (iii) convulsion therapy; (iv) treatment of the epilepsies; (v) chemical sedation and stimulation; (vi) continuous sleep treatment; (vii) the use of drugs in psychotherapy; (viii) diet, vitamins and endocrines; (ix) prefrontal leucotomy; (x) the treatment of general paralysis; (xi) the relation of psychological to somatic treatment. Bibliography. Index.

The success of this comprehensive manual of psychiatric therapies, as shown by the appearance of this 2nd, revised edition, is first and foremost due to the full, lucid descriptions and explanations of the various more or less novel methods of physical treatments. They are taught by experts who speak from their own wide practical experience and the reader has the feeling that he makes contact, not with literature, but with the physician used to applying the treatment he describes. From the first sensational success of physical treatment in psychiatry 30 years ago—the malaria treatment of general paresis— all those therapeutic procedures which have stood the test of time and have become reliable adjuncts of psychiatric work in hospitals are dealt with: the various uses of insulin and hypoglycaemic treatment, convulsive therapy in its different modifications, chemical sedation, treatment by diet, vitamins and endocrines, and prefrontal leucotomy. In the new edition of this book the methods are brought up to date and new techniques, such as the abreaction methods using drugs, have been added and are fully discussed. Another important addition is the chapter on the treatment of epilepsy, written by Dr Denis Hill, who has incorporated recent progress on the theory of this illness as well as the practical application of electroencephalography into his clear and skilfully written discourse.

Beyond its practical usefulness, the present small book has the distinction of representing a new approach to psychiatry which has gained it many friends: the authors' restrained enthusiasm for active integration of psychiatry into clinical medicine and away from speculative and philosophical doctrines. In the introductory chapter as well as in the concluding part on the relation of psychological to somatic treatment this approach finds a concise and striking expression. These chapters, in fact, contain a psychiatric theory in a nutshell; this theory deserves elaboration and application on a much larger scale.

W. Mayer-Gross

1589 Psycho-Analysis. A Handbook for Medical Practitioners and Students of Comparative Psychology

Edward Glover. Second edition. London: Staples Press, 1949. 367 pages. 22 × 14 cm. 15s. [£0.75]

(i) Introductory. Section I. Theory of psycho-analysis. (ii) The embryology of mind; (iii) the dynamic aspects of mind; (iv) the structure of mind; (v) the economics of mind; (vi) phases of mental development; (vii) dreams and symptomatic acts; (viii) symptom formation. Section II. Clinical psychoanalysis. (ix) Introductory; (x) psycho-neuroses; (xi) psycho-somatic and allied disorders; (xii) psychoses; (xiii) transitional groups; (xiv) psychosexual disorders; (xv) social difficulties; (xvi) psycho-analysis of children. Section III. (xvii) Practical applications. Appendix. Glossary. List of books recommended. Index.

In his preface to this 2nd edition the author welcomes the opportunity of re-stating the basic theory of psychoanalysis but, in fact, the chapters on theoretical subjects occupy less than one-third of the book and are followed by a survey of the clinical field. There is much sound advice to general medical practitioners on the applicability of psychoanalytic methods of treatment. Finally, the book contains a useful glossary of psychoanalytic terms and a guide to the literature.

Glover claims that psychoanalysis is not merely a method of treatment, but that it has become an instrument of "diagnosis in depth" by applying the developmental approach to the classification of mental diseases. It has also been turned into an instrument of research and has produced a theory of mind—by utilizing three approaches to the full understanding of every mental event. In the topographic approach, Freud based his theory of mental structure on the concept of the reflex arc, with mind as the central system subdivided into a number of component parts, the mental institutions. The second, dynamic, approach deals with the excitations which disturb this central system, e.g., stimulations of unsatisfied instincts which produce either mental experiences (thoughts and feelings) or motor discharges which make up conduct and behaviour. Finally, mental activity may be regarded as an economic process, by which the psychic apparatus attempts to deal with instinct excitations which cannot be immediately discharged and which might produce discomforts, such as anxiety. The mind seeks to reduce stimulation and, on the other hand, deals with undischarged excitations by means of a number of mental mechanisms. Normality depends upon the degree of success which attends these manoeuvres, and this economic approach confirms that normality is an artificial concept and that "neuroses and other mental disorders are simply forms of unsatisfactory (inappropriate, unrealistic) discharges which occur when the individual has been unable to achieve a working balance between his instinct-tensions and the outlets permitted them either by himself or by his social environment". Psychological symptoms are regarded as "mental policies" to resolve conflicts between inner drives and wishes with outer reality; they may even be looked upon as "in part a spontaneous attempt at self-cure".

In addition to the further elaboration of these theories and their clinical application, the book contains numerous references to recent psychoanalytic work and concepts. Among these should be mentioned Glover's own contribution to ego development, in which he suggests that ego nuclei are laid down during the successive stages of development of instinct. These nuclei are looked upon as organized systems of memory traces and ideations contributing at first to the gratification and later to the control of specific instincts. The author admits the hypothetical nature of many central psychoanalytical tenets, especially those relying on interpretations of phenomena observed during the first 18 months of life, and yet at the same time he seems to accept as the only important inborn constitutional factor the individual's ability to tolerate frustration. The clinical part of the book contains a comprehensive account of the psychoanalytic contribution to the understanding and treatment of psychiatric disorders, ranging from the classical neuroses and psychoses, through the drug addictions, psychosomatic conditions and psychosexual disorders, to disabilities primarily of social rather than medical importance.

Very little space is given to a discussion of the methods of psychoanalytic research and of the way in which Freud and his pupils arrived at their theories, and it must, therefore, be assumed that this book is addressed to a reader who is already acquainted with psychoanalytic thinking; he will, however, find much to clarify his understanding of the theory and present-day trends of orthodox Freudian psychoanalysis.

Felix Post

1590 Psychobiology and Psychiatry. A Textbook of Normal and Abnormal Human Behavior

Wendell Muncie. Second edition. London: Henry Kimpton, 1948. 620 pages; 70 illustrations. 26 × 18 cm. £2 5s. [£2.25]

Part I. Psychobiology—the study of normal behavior. (i) Historical and philosophical bases of psychobiology; (ii) student's personality study; (iii) student's personality study (*continued*); (iv) student's personality study (*continued*). Part II. Abnormal behavior—pathology and psychiatry. (i) Historical account; (ii) examination methods and immediate findings; (iii) the static constitutional types; (iv) plastic psychodynamic minor reactions; (v) plastic psychodynamic minor reactions (*continued*); (vi) major reactions (holergasias); (vii) affective reactions; (viii) affective reactions (*continued*); (ix) topical delusional states and para-reactions; (x) para-reactions (*continued*); (xi) the support disorders (dysergasia); (xii) the acquired organic deficit reactions (anergasia); (xiii) the acquired organic deficit reactions (anergasia) (*continued*); (xiv) the convulsive state and allied conditions (the epilepsies). Part III. Treatment. (i) General bases of treatment and the procedure; (ii) important therapeutic aids; (iii) important therapeutic aids (*continued*); (iv) treatment of the static constitutional reactions; (v) treatment of the psychodynamic minor reactions: psychoneuroses; (vi) treatment of the major reactions (holergasias); (vii) para-reactions; (viii) dysergasic reactions; (ix) organic deficit states; (x) treatment of convulsive disorders (the epilepsies); (xi) mental hygiene. Index.

The 1st edition of this American textbook for students appeared in 1939. The author is an Associate Professor of Psychiatry at Johns Hopkins University and he has worked with Adolf Meyer for almost 20 years. The book was welcomed as an authoritative account of the school of psychobiology, especially as the teaching of Meyer had been handed on mainly by word of mouth and no full and definitive version had previously been available, although the standard English textbook of Henderson & Gillespie was inspired by Meyer's views. Both in North America and in Britain these views have had an enormous influence on psychiatry, although they have received less attention on the continent of Europe where Meyer lived for the early part of his life. At a time when the opposing views of Kraepelin and Freud held the field, Meyer developed an eclectic approach which kept to the broad middle of the road. He regarded mental disorder as an "experiment of nature" and for him genetic-dynamic considerations took the place of hidden etiological factors; all the relevant exogenous, organogenic, neurogenic, psychogenic and constitutional elements in the individual were considered and evaluated. Unfortunately, in the exhaustive search for the patient's personality his disease tended to be overlooked. Thus the need for exactitude in diagnosis and prognosis was minimized, and treatment became similarly inexact and opportunistic. In diseases such as schizophrenia the followers of Meyer spent much time in tracing the development of the disease from a series of life-long maladaptations to various psychological and physical traumata, and they spent even more time in unrewarding efforts to treat schizophrenia by re-education. In the understanding and treatment of the superficial neuroses the Meyerian approach has borne more fruit.

These criticisms are criticisms of psychobiology; as an exposition of psychobiology, no adverse criticisms can be made of this book. In the first part, of 136 pages, the student is introduced to the study of personality in its longitudinal development and he is set useful exercises in self-appraisal. The second part, of 378 pages, describes the neuroses and psychoses, and numerous case-histories illustrate the psychobiological approach. The final part, of 94 pages, describes therapy. This 2nd edition has been brought up to date but is essentially unchanged from 1939. It gives a complete and readable picture of the work of Adolf Meyer, whose hitherto paramount influence on Anglo-American psychiatric thought is being lessened by the advance of other schools.

Hunter Gillies

1591 Conditioned Reflexes and Neuron Organization

Jerzy Konorski. Cambridge: University Press, 1948. xiv + 267 pages; 18 figures. 22 × 14 cm. 18s. [£0.9]

(i) Conditioned reflexes and the physiology of the central nervous system; (ii) an outline of Pavlov's theory of the activity of the cerebral cortex; (iii) a criticism of the Pavlov theory. Addendum: the Beritoff theory; (iv) general laws of the functioning of the nervous system; (v) excitability and plasticity in the nervous system; (vi) the conditioned reflex; (vii) alliances and antagonisms in the field of conditioned reflexes. (The summation of conditioned reflexes and external inhibition); (viii) the generalization of conditioned reflexes; (ix) internal inhibition. 1. Its nature and varieties; (x) internal inhibition. 2. The basic properties of inhibition. Addendum: on the phenomenon of sleep; (xi) the dynamic stereotype and hypnotic phases; (xii) conditioned reflexes of the second type; (xiii) nomenclature of the physiology of higher nervous activity; (xiv) conclusion. Index.

The acknowledged aim of this book is to build a bridge between Pavlov's massive, if somewhat insecure, theoretical edifice and the

more solid structure of Sherringtonian neurophysiology. This task is far from easy. As the author himself points out, the whole style of Pavlov's doctrine is foreign to traditional physiological thought. In particular, the neurone theory, with all that it implies for contemporary neurophysiology, finds no essential place in Pavlov's system. Although it might be possible, by special pleading, to reconcile some aspects of the latter with more orthodox conceptions of nervous activity, Dr Konorski has set himself the harder, but infinitely more rewarding, task of reinterpreting the whole of the data so painstakingly assembled by Pavlov and his school in the light of Sherringtonian principles. Even if he does not entirely succeed, no reader of this book can deny that he has tried extremely hard and, on the whole, extremely intelligently.

After a preliminary outline and critique of Pavlov's main theories, Dr Konorski undertakes a detailed examination of conditioned reflexes and their more important properties. The formation of a conditioned reflex he views in terms of the establishment of new synaptic connexions (presumably functional) between the cerebral " centres " involved. This is certainly an improvement on Pavlov's disconcertingly vague conception of the association process. In somewhat the same way, he regards internal inhibition as involving the formation of new and independent synaptic connexions of an inhibitory character. On this view, when a conditioned reflex is extinguished, a new inhibitory reflex is built up in such a way that, when the conditioned stimulus is applied, its cortical locus emits both excitatory and inhibitory impulses to the " centre " corresponding to the unconditioned stimulus. The magnitude of the resulting response will then depend on the relative density of the two hypothetical volleys of impulses. Although somewhat speculative, this is certainly a better idea than Pavlov's notion of an inhibitory process irradiating in some obscure manner from the central locus of the conditioned stimulus. Even so, it must be borne in mind that Konorski's hypothesis, although agreeing well with certain experimental data, at bottom does little more than postulate that, in the conditioning process, *some* change in cortical synaptic conduction patterns is involved. Its reception will presumably depend upon the extent to which it can stimulate fruitful experimental inquiry.

After a long theoretical discussion of various other conditioning phenomena, such as generalization and summation, the author passes on to some aspects of Pavlov's work relatively little known in this country. These do much to relate the fragmentary reactions studied by the classical conditioning technique to broader problems of behaviour. Thus it was shown by Pavlov himself that " . . . in conditioned reflex experiments each trial is not an independent event but forms a certain whole with other trials." This he termed the " dynamic stereotype ". It is adduced to explain such facts as that when a system of conditioned stimuli is repeated daily for a long period in the same order of succession, a change in the sequence of the stimuli will produce comparatively little effect upon the response. If, for example, a strong stimulus is replaced by a weak one its effect will nevertheless be strong. Dr Konorski devotes some interesting discussion to " temporal patterning " of this kind which will do much to mollify those who have taken Pavlov to task for his apparent neglect of " gestalt " principles.

Dr Konorski's book is perhaps the first critical examination of the theory of the conditioned reflex to appear from one who was himself trained in the strict Pavlovian school. As might be expected, it testifies to a wide and intensive knowledge of the original literature. It is evident, too, that the author is first and foremost an experimentalist who was led to undertake this inquiry less from pure theoretical interest than from a wish to disentangle fact from dogma and so to free the road for fresh empirical research. Although Dr Konorski cannot rank as a theorist of the first order, his brave and scholarly book deserves close scrutiny. Despite its difficult and somewhat abstruse style, it will remain as a notable attempt to pierce the " iron curtain " of Soviet science and to relate what is most valuable in Pavlov's work to the general development of neurophysiology.

O. L. Zangwill

1592 Neurological Anatomy in Relation to Clinical Medicine

A. Brodal. Oxford: Clarendon Press; London: Geoffrey Cumberlege, 1948. xv + 496 pages; 94 figures. 25 × 16 cm. £2 2s. [£2.1]

(i) Introduction, methods, correlations; (ii) the peripheral motor neuron; (iii) the pyramidal tract; (iv) the extra-pyramidal system; (v) the cerebellum; (vi) the somatic afferent system; (vii) the cranial nerves; (viii) the optic system; (ix) the acoustic system; (x) the olfactory system; (xi) the autonomic nervous system; (xii) the cerebral cortex. Bibliography. Index.

This book, which first appeared in Norwegian in 1943, is an attempt to correlate the anatomy and physiology of the nervous system with clinical neurology. It was designed to be an up-to-date vade mecum for the clinical neurologist. It therefore omits most of the simple anatomy which one finds in the ordinary textbooks of neuro-anatomy and also omits most of the basic facts of neurophysiology. Such a book has the merit of placing the reader in contact with much recent work, both experimental and clinical, and saves the labour of hunting through the recent journals. The author successfully runs the risk of putting into italics any statements of fundamental value which are now verifiable postulates.

On the other hand, the very newness of the data tends to militate against the ordered historical perspective of the development of clinical neurology. Many of the new data are hot from the press, but they may not all stand the test of time. *Difficilis est sigellum veritatis*, particularly in neurology.

The introduction deals with the laboratory, experimental and clinical methods of the subject and then proceeds to deal in sequence with the lower motor neurone, the pyramidal tract, the extra-pyramidal system and the cerebellum. This is followed by chapters which deal in turn with the somatic afferent system, the cranial nerves, the optic system, the acoustic system and the olfactory system. The remaining two chapters deal with the autonomic system and the cerebral cortex. Thus the order of presentation, successful though it be, bears little relationship to the phylogenetic or ontogenetic development of the nervous system. The author is naturally at his best when dealing with his own well-known researches on the cerebellum. The section on the autonomic system is the most comprehensive in terms of space.

The reading of this book compelled the reviewer to re-read Romberg's *Lehrbuch der Nervenkrankheiten* (1840–46), Horsley's *Fullerian lectures for 1891* (1892) and Llewellys Barker's *The nervous system* (1900), and to conjecture whether in the near future we may have a book on clinical neurology based on the simple functional classification of Horsley. The latter maintained that the five kinds of function to be provided for were: (i) movement; (ii) sensation; (iii) tone; (iv) nerve supply to the blood vessels; (v) secretion.

The present volume by Brodal is timely and collects together much work of the last two decades. The illustrations are purposive and concise. The English is clear. No clinical or laboratory library can afford to be without this book.

H. A. Harris

1593 Pathology of the Nervous System. A Student's Introduction

J. Henry Biggart. Second edition. Edinburgh: E. & S. Livingstone Ltd., 1949. xii + 352 pages; 232 figures; 10 coloured plates. 22 × 14 cm. £1 1s. [£1.05]

(i) The neurone and its reactions to disease; (ii) the reactions of the interstitial cells to disease; (iii) the cerebrospinal fluid in disease; (iv) vascular disease and the brain; (v) acute bacterial disease; (vi) chronic infections; (vii) diseases due to viruses; (viii) diseases of unknown etiology, possibly infective; (ix) intoxications and deficiency diseases; (x) degenerative diseases; (xi) injuries to the nervous system; (xii) tumours of the nervous system; (xiii) tumours of the nervous system (*continued*); (xiv) errors in development. Index.

As the quotation given by the author on the fly-leaf of this book says: " The study of things caused must precede the study of the causes of things ! " Whilst recent knowledge of the latter is adequately summarized, emphasis is laid upon the morbid anatomy and histology of the common and important pathological conditions. The student, for whom the book is still intended as an introduction to neuropathology, gains much from the knowledge of general pathology possessed by Professor Biggart. A remarkable amount of information is contained within the covers of this excellent book, which, in spite of additional text and figures, is only 17 pages longer than the 1st edition. The use of coloured plates is very helpful, especially in the section on pituitary tumours. The new matter includes sarcoidosis, parasitic and fungal infections and polyarteritis nodosa. At the end of each chapter there is a short bibliography, which does not, unfortunately for the more

serious student, contain all the papers considered important enough to be mentioned in the text. It is not quite clear from the text that obstruction to large cerebral arteries causes ischaemic necrosis not only of the cortex but also of a wedge-shaped portion of underlying white matter. The presentation of the book is of the excellence one associates with Messrs Livingstone, but there would be advantages in a larger page: illustrations and relevant text are more often visible together and there is less frequent turning of pages. In spite, however, of these criticisms it remains one of the best books on neuropathology, not only for students but also for their seniors.

W. Blackwood

SOCIAL MEDICINE

1594 Mental Health Services. A Handbook on Lunacy and Mental Treatment and Mental Deficiency

F. B. Matthews. London: Shaw & Sons Ltd. [1949]. vi + 483 pages. 22 × 14 cm. £1 15s. [£1.75]

(i) Introduction; (ii) mental defectives and persons of unsound mind; (iii) the administrative structure—central and local; (iv) the powers and duties of the administrative bodies; (v) discharge of patients from detention. Appendix I: Lunacy, mental treatment and mental deficiency Acts, as amended. Appendix II: Lunacy, mental treatment and mental deficiency Orders, Rules and Regulations. Appendix III: Miscellaneous Acts and Orders, etc., dealing with mental patients or their income. Index.

This is a legal handbook dealing with the very complicated statutory law concerned with lunacy and mental deficiency in England and Wales. There is an excellent introduction, historical in character, and illuminating for those not familiar with the background of the development of legislation. Essentially a reference work, this book would appear to be by far the most comprehensive and accessible source of information now available, and is especially suitable for officers of mental hospitals, members of [illegible]spital boards, and medical officers of health. The illuminating notes, the attention to accurate detail, and the great care which has been given to devising a logical arrangement make the book unique; and the author manages, nevertheless, to call the reader's attention continuously to the main purposes for which the legislation was formed.

With the passing of the last remnants of the Poor Law and the disappearance of the officials who for so long had rather illogical statutory duties in "lunacy" and mental deficiency procedure, the time is particularly opportune for a re-statement of the law. No matter how drastic the change in social legislation in Britain and no matter how great the necessity appears for complete re-statement, a complete codification of the law in a single statute is never achieved nor, indeed, ever appears really seriously to be attempted.

Before the National Health Service Act of 1946, the major local authorities had become accustomed to administering the law regarding mental defectives and persons of unsound mind. Even if responsibilities were divided between departments, and if the provision of the old Poor Law sometimes entailed curious variations in practice, these local authorities dealt with all aspects of the problems of mental health. Now the public assistance committees and their officials who administered the Poor Law have gone, the mental institutions have passed to the Regional Hospital Boards, and there have been and still may be minor difficulties.

It seems to the reviewer that the intelligent use of this book should enable anyone in doubt to find the powers to take action and procedure for all the difficult situations which arise in practice.

Alan C. Stevenson

1595 Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Sixth Revision of the International Lists of Diseases and Causes of Death, Adopted 1948. Volume 1

World Health Organization. Geneva: World Health Organization, 1948. (*Bulletin of the World Health Organization*, Supplement 1.) xxxvii + 376 pages. 24 × 16 cm.

(i) Introduction; (ii) list of three-digit categories (detailed list); (iii) tabular list of inclusions and four-digit subcategories; (iv) medical certification and rules for classification; (v) special lists for tabulation; (vi) suggested form of multiple-cause tabulation; (vii) regulations.

This is the first volume of a two-volume statistical classification and index of diseases, injuries and causes of death. It follows the tradition established by the International List of Causes of Death and synthesizes the varied experiences of different countries in their use of the 1938 International List. Compiled by a group of recognized experts on health statistics, it represents the logical result of efforts dating from 1853 directed towards an internationally accepted classification upon which comparable statistics relating to causes of illness and death can be based. The classification is an improvement upon all previous lists in that it is designed for morbidity as well as mortality statistics, and, by its unanimous acceptance at the Sixth Decennial Revision Conference held in Paris in April 1948, wider international agreement than before has been achieved as to its use. The international agreement extends to details of tabulation and to standard groupings of diagnoses.

Volume I contains the classification itself and sets out the detailed categories and sub-categories of causes of illness and death, together with a supplementary classification of special admissions, live births, stillbirths, prophylactic inoculation, impairments, blindness and deafness. There is a section on medical certification and rules for classification, and other relevant material. There are 17 headings in the main classification which contain in detail some 612 categories of morbid conditions. The disease rubrics of the previous International List have been expanded to provide special categories for non-fatal diseases and injuries, whilst at the same time permitting comparability with certain categories of the preceding International List.

Volume II will provide a comprehensive alphabetical index to the classification in Volume I. At present it is a difficult matter to code some diseases and conditions. Several users of the *Manual*, however, are of opinion that when this index is available the classification will leave little to be desired, although further opinion based on its full practical application will be awaited with interest. The *Manual*, which must represent an enormous amount of work, contains several special aspects which warrant notice, particularly the section which covers accidents, poisons and violence, because here there is a departure from previous methods of classification and coding.

"The World Health Organization is offering this *Manual* in the hope and expectation that it will be, not merely an object of interest to medical statisticians, but the instrument for collecting information into a common pool of knowledge from which, in time, all mankind will benefit." This quotation from the preface to the volume makes the character and the aim of the classification clear.

L. E. Griffith

1596 The Design and Equipment of Hospitals

Ronald Ward. London: Baillière, Tindall & Cox, 1949. xvi + 360 pages; 177 figures; 50 plates. 25 × 19 cm. £2 2s. [£2.1]

(i) Introductory; (ii) general considerations; (iii) administrative considerations; (iv) medical considerations; (v) special wards; (vi) special hospitals; (vii) construction. Conclusion. Bibliography. Index.

This book, published at an appropriate moment following the inauguration of the National Health Service and in anticipation of

a revival of hospital building projects, provides a wealth of information of practical use to all who are interested in modern trends of hospital design and in the development of the hospital and public health services.

It is intended for doctors, hospital administrators, public health officials and architects. It provides guidance also for members of boards and committees in their consideration of building schemes and the policies involved. Though hardly to be classed as popular reading it will repay perusal by non-technical members of the public, and it should be welcomed particularly by students and by younger members of the architectural profession who intend to specialize in hospital design and who hitherto may have found the search for adequate and essential data on the subject to be somewhat arduous. The arrangement of the contents and the well-compiled index render the book useful for ready reference to any particular point.

The introductory section deals with general considerations of the hospital as it existed before the passing of the National Health Service Act, 1946, and with the formulation of hospital building schemes. The procedure relating to such schemes is described, and broadly meets the present position under the National Health Service Act; the main differences arise from the fact that the majority of hospitals are now vested in the Minister of Health and expenditure upon them is included in the annual estimates of the Ministry and is met by the Treasury, whose consent is necessary before expenditure is made on proposals costing over £10,000.

In the second section, the site and lay-out of the hospital, horizontal versus vertical planning, sizes of wards, orientation, interrelation of the various units and so on are dealt with. The advantages and disadvantages set forth provide useful material for discussion and final decision. The need for collaboration between the architect, the doctor, the administrator, and the heads of administrative, nursing and other departments is emphasized, with a view to ensuring that the hospital will meet fully the needs of the patients and will simplify the work of those engaged in their treatment and care.

The general hospital is comprehensively described and although some special hospitals, e.g., the mental hospital, receive less attention, the principles of planning are set out in such detail that their application, with such modification as is necessary to meet special needs, should not entail any great difficulty to those concerned. The frequent references in various sections to planning simple and beautiful buildings, of architectural interest externally and internally, in pleasant surroundings, and with colour schemes which have soothing effects upon the patients, are summarized in the conclusion.

The book is illustrated with diagrammatic plans and photographs of interiors, and provides a general survey of the present trends in design. It is worthy of study by all who have at heart the welfare of the sick. Sufficient mention is made of standardization to show the dangers of stereotyped planning which can hinder progress; though some standardization of fittings and equipment may effect saving in cost, the need for continual research and experiment in planning and equipment, to effect still greater advances and improvement, is imperative. Readers may disagree with many of the views expressed; this is not undesirable, however, as it may lead to discussion of these views and to further efforts to improve upon them in an endeavour to attain the ever-elusive perfection.

F. C. W.

1597 Hadden's Health and Welfare Services Handbook. Being a General Guide to the Law Relating to the Health and Welfare Services Administered by Local Authorities, Together with National Insurance and National Assistance

John Moss. London: Hadden, Best & Co. Ltd., 1948. xxi + 376 pages. 19 × 12 cm. £1 5s. [£1.25]

(i) Central and local authorities; (ii) provision of residential accommodation; (iii) local authority welfare services; (iv) local authority officers; (v) liability for maintenance; (vi) mental health service; (vii) the care of children; (viii) National Insurance benefits; (ix) National Assistance and non-contributory schemes. Appendix A: National Assistance Act, 1948 (extract from Ministry of Health Circular 87/38, June 7, 1948). Appendix B: National Assistance Act, 1948 (Second Schedule). Index.

The passage of the National Health Service Act, 1946, the National Assistance Act, 1948, and, to a lesser degree, the Children Act, 1948, has laid upon local authorities new and complex duties. Mr Moss's handbook sets out these duties in a simple and easy form, and, at the same time, shows how important it is for anyone who wishes fully to grasp the potentialities and significance of these Acts to have some understanding of the various schemes of national insurance provided by the National Insurance Act, 1946, and the National Insurance (Industrial Injuries) Act, 1946. The book reviewed here provides a short, but clear and admirable, guide to all this complicated legislation; the appearance of Mr Moss's name upon the title-page is the best guarantee of its excellence.

One of the results of the break-up of the Poor Law has been the development of a too rigid separation between those who need residential accommodation because they are sick, e.g., in hospital under the Regional Hospital Boards, or Boards of Governors, and those who need it because they are destitute, using the word in its broadest sense, e.g., in accommodation provided under Part III of the National Assistance Act, where local authorities are required to make provision for persons who "... by reason of age, infirmity or other circumstances are in need of care and attention". Under the Poor Law the Relieving Officer could arrange accommodation for all who needed it. This accommodation was often not ideal, but at least a roof, bed, food and nursing were available. Now there is emerging a type of person whom the Regional Hospital Board or Board of Governors will not accept because they are not really ill, yet who are too infirm to be accommodated in an institution or hostel for the healthy. Ultimately they will be dealt with under Part III of the National Assistance Act, but even when the provisions of the local authority services are available to the full, it will be necessary to have the closest co-operation between the Regional Hospital Boards and Boards of Governors and the local authority so that a patient who is being accommodated under the provisions of Part III can be easily transferred to a hospital, and a hospital patient who is not in need of full medical and nursing care similarly transferred to accommodation under Part III. Mr Moss rightly emphasizes the importance of this "two-way" traffic, which is, indeed, the only way to ensure the continuance of an excellent principle that was inherent in the Poor Law, whereby patients could move easily from workhouse to hospital as their condition required. Failure to secure this co-operation would lead to the development of a new type of infirmary where the chronic, or long-term sick, would lie for years with little or no medical attention.

There is also a danger that the substitution of 300 area offices of the National Assistance Board for some 1,500 Relief Districts will make it more difficult for the old and the destitute, if "relief" is to be used in its fullest sense, meaning that it can be obtained in an emergency, when it is needed most. The Relieving Officer resided in his district, and being personally responsible for what went on in that district, knew the people most likely to be in need of relief, and maintained what was, to all intents and purposes, a 24-hour service. As Mr Moss points out, such a service cannot be restricted to ordinary office hours, but the 24-hour service will be more difficult to maintain when it is administered from a number of central offices.

The other important change that is discussed in this book is the new situation that has arisen with the passing of the Children Act, 1948. Under this, a special officer, the Children's Officer, is appointed to look after the welfare and interest of those children who have been deprived, for one reason or another, of normal home life and parental care. The admirable intention of this Act was to bring up these children, living in accommodation provided by the local authority, in as normal and happy a way as possible. The health and education departments of a county or county borough council deal with normal children at varying stages of their life, and it might have been wiser if the Children's Officer had been a member of the staff of one or other of these departments, preferably of the former, and thus to have assured that these unfortunates, with all other children, would have been the responsibility of the same department of the council. This would have assisted in enabling them to live as normal a life as possible and to grow into normal adults.

Mr Moss's book is clearly written and well indexed, with a wealth of reference to the Statutes and to the many Regulations and Orders made under them. Certainly no local authority can afford to be without this book, and anyone working in the field of welfare today will find it a valuable possession.

Amulree

1598 Taylor's Principles and Practice of Medical Jurisprudence. Volume II

Originally written by *Alfred Swaine Taylor*. Tenth edition edited by Sydney Smith, with a complete revision of the legal aspect by W. G. H. Cook and of the chemical aspect by C. P. Stewart. London: J. & A. Churchill Ltd., 1948. vii + 841 pages; 7 illustrations. 25 × 16 cm. £2 10s. [£2.5]

Part I. Sexual medical jurisprudence, obstetric and criminal. (i) Impotence and sterility; (ii) virginity and defloration; (iii) pregnancy; (iv) delivery; (v) dissolution and nullity of marriage; (vi) legitimacy and paternity; (vii) rape; (viii) abortion; (ix) natural birth and medico-legal questions connected therewith; (x) infanticide; (xi) unnatural offences. Part II. Poisoning and toxicology. (xii) The law of poisons, including the definition of a poison or noxious thing; (xiii) dangerous drugs; (xiv) the action of poisons and the circumstances which influence it; (xv) diagnosis of poisoning; (xvi) what to do in cases of poisoning; (xvii) classification of poisons. A chapter on medical jurisprudence in India. Appendix: the rhesus factor. Index.

The 10th edition of this work,[1] although retaining the principal features of "Taylor," has been thoroughly revised and brought up to date. In some parts, the arrangement of the book has been slightly altered, and certain sections have been completely rewritten; a considerable quantity of fresh material has been added.

Volume II of the work, which is considered here, is divided into Part I, which treats the wide subject of sexual medical jurisprudence, and Part II, which covers the field of toxicology. The sexual subjects include impotence and sterility, nullity of marriage, pregnancy, rape, abortion, infanticide, and unnatural offences. Each of these sections includes appropriate decisions of English Courts of Law.

The section on toxicology deals with the law controlling the sale of poisons, including a description of the various poisons and their actions; it also describes the diagnosis and treatment of poisoning and the post-mortem findings in fatal cases. It is unfortunate that the list of drugs composing the Fourth Schedule of the Pharmacy and Poisons Act, 1933, and the list of dangerous drugs as set out in the Dangerous Drugs Act, 1932, have not been brought up to date, and that the omissions from these lists should include such drugs as tridione and pethidine, respectively. The accounts of the mode of action and symptomatology of the various poisons are very well represented and are most informative. It seems odd that, in a book of this size, there should be a complete absence of photographic plates.

Those responsible for the revision and editing of this second volume have to be congratulated on their success in completing such a difficult task.

John Glaister

[1] For review of Vol. I see *BMB* 1355 (*Brit. med. Bull.* 1949, 6, 99).—ED.

MEDICAL SCIENCES & RESEARCH

1599 The Mammalian Adrenal Gland

Geoffrey H. Bourne. Oxford: Clarendon Press, 1949. vi + 239 pages; 226 figures; 15 plates. 24 × 16 cm. £1 10s. [£1.5]

(i) Historical; (ii) vertebrate adrenals and classification of mammals; (iii) the adrenals of the monotremata; (iv) the adrenals of the metatheria; (v) the adrenals of the eutheria; (vi) general summary of mammalian adrenals. Bibliography. Index. Plates.

If, as far as endocrinology is concerned, the twenties of this century were the decade of insulin and thyroxin, the thirties the decade of the sex hormones, the forties the decade of the anterior pituitary, then all the signs indicate that the fifties are likely to be the decade of the adrenal cortex. Though Addison's famous clinical study of adrenal deficiency provided one of the opening chapters of the long story of endocrinology, the complex pattern of the participation of the adrenal cortex in a variety of physiological functions is only now being unravelled. Intensive work on the chemistry and physiological function of the numerous steroids secreted by, or at least obtainable from, the adrenal cortex, hitherto rather a close preserve of the specialist, and presenting by its very complexities a somewhat forbidding aspect to the general biologist, has recently been illumined by the spectacular discovery of incalculable therapeutic possibilities for the application of one of the cortical steroids as a palliative for one of the most intractable and crippling diseases which afflict mankind, rheumatoid arthritis. This discovery seems likely to appeal to the public imagination in the same way as did the discovery of insulin, and there is no doubt that scientific attention is likely to be focused on the adrenal gland for a long time to come. This being so, the recent appearance of one or two books dealing with this endocrine gland, of which Dr Bourne's is one, can be considered timely.

At the outset it should be said that the title of Dr Bourne's monograph is not as informative as it might well have been. An abbreviated title of such general implication might lead the reader to expect a treatise dealing not only with the anatomy but also with the physiology, pharmacology and metabolic functions of the adrenal and especially of the cortex. In fact, as the author explains in his preface, it is based largely on material submitted many years ago for the degree of D.Sc., and this, the main theme of the book, comprises a comparative study of the anatomy of the adrenal gland in a wide variety of mammalian forms. A monograph of this type is usually caviare to biologists in general, since by its very nature it is addressed to specialists, for whom it constitutes a valuable source of reference. For this reason such monographs are often not easy to get published, and when they are published the price is apt to be high. Happily this is not the case with the book under review.

The first chapter is historical and opens, in the reviewer's opinion mistakenly, with a passage in Latin of which no translation is provided. Another Latin quotation follows hard on the heels of the first. This is apt to be irritating to readers educated by those who do not consider an ability to read obsolete Mediterranean languages as necessarily an essential ingredient of a good education. Other descriptive chapters follow in which the anatomy of the adrenal gland in various mammalian species is considered, often rather catalogue-wise. At times one may detect a certain emphasis on Australian mammals, which perhaps reflects the author's own interests. Many of the descriptions are given here for the first time by the author and descriptions given by others are discussed where appropriate. One feels that in some cases the description is based on too few specimens to carry full conviction while often, as the author is careful to point out, the material is far from ideal for histological study, having been taken from museum specimens after many years in preservative. Nevertheless we have here a conspectus of much out-of-the-way descriptive data which may well be of interest to other specialists in this field.

The material of more general and immediate interest to the endocrinologist is confined to a final chapter entitled "General summary of mammalian adrenals." This chapter, besides embodying a general summary, one might say an attempted synthesis, of what has gone before, includes brief surveys of the physiology of cortex and medulla. The general nature of the book's title, already referred to, might well have led the reader to expect more extensive treatment of what is at the present time very much a live experimental subject, as attested by the number of symposia and reviews on adrenal cortex endocrinology which have appeared in recent years. Effective use could have been made of these in expanding this part of the book without necessarily swamping the anatomical section, with an enhancement of the value of the book and a widening of its appeal. This final chapter also includes an excursion along the perilous path of attempting to deduce evolutionary relationships (with particular reference to marsupials) from the anatomical position of the adrenal glands. Such speculations are always interesting, seem a peculiarly fruitful cause of lively, even heated, controversy, and are justified provided the conclusions are not too finely drawn.

As is to be expected from this publisher, the volume is a good piece of book-making. Unfortunately lack of care in proof reading is evidenced by too frequent occurrence of errors in spelling. Authors' initials are omitted from the bibliography, which is a pity,

and mistakes in the spelling of authors' names can be detected in text and bibliography alike. A high standard of bibliographic accuracy is nowadays a generally agreed desideratum in a scientific monograph and it is to be hoped that these blemishes will be rectified if a 2nd edition is called for.

S. J. Folley

1600 Diagnosis of Viral and Rickettsial Infections. Symposium Held at the New York Academy of Medicine, January 29 and 30, 1948

Edited by *Frank L. Horsfall*. New York: Columbia University Press; London: Geoffrey Cumberlege, 1949. x + 153 pages; illustrations. 23 × 15 cm. £1 1s. [£1.05]

(i) Introduction; (ii) laboratory diagnostic procedures for influenza; (iii) the diagnosis of mumps; (iv) the diagnosis of infections caused by the psittacosis-lymphogranuloma group of viruses, including trachoma and inclusion blennorrhea; (v) the diagnosis of primary atypical pneumonia; (vi) the diagnosis of neurotropic virus infections, including the viral encephalitides, lymphocytic choriomeningitis, and poliomyelitis; (vii) the diagnosis of infection with the virus of herpes simplex; (viii) the diagnosis of rabies; (ix) the diagnosis of dengue; (x) the diagnosis of infectious mononucleosis; (xi) the diagnosis of epidemic, murine, and scrub typhus, as well as Q fever; (xii) the diagnosis of Rocky Mountain spotted fever and rickettsialpox; (xiii) the diagnosis of infectious hepatitis.

Considerable advances in the laboratory diagnosis of virus diseases have been made in the past 10 years. Although many of the techniques and tests used require slightly different equipment and training from that necessary in routine bacteriological laboratories, facilities are being made more widely available in special laboratories for the use of doctors in hospitals and general practice. The laboratory diagnosis, except in the case of smallpox, is not usually available until too late in the progress of the disease to be of practical value in the individual case, but is of considerable help in investigating epidemiological and public health problems. There have been several recent American publications on the clinical aspects and diagnosis of virus and rickettsial diseases, but the New York Academy of Medicine obviously considered that there was a place for this handy small volume of 153 pages. Most of the authors who delivered papers at the symposium held at this Academy have already contributed similar material to other books.

One of the most useful chapters is that on primary atypical pneumonia, where the unsatisfactory position with regard to this broad group of infectious diseases is clearly set out by Horsfall, who edited the volume.

There is a striking omission of any instruction on the collection of material for the diagnosis of smallpox, although the symposium took place after a series of cases in New York in 1947. The diagnosis and control of the pox group of diseases is one of the main public health problems over a considerable part of the globe. On the other hand, there is a chapter on infectious hepatitis, although no specific in vitro test or susceptible experimental animal has been found for this presumed virus infection.

Most chapters follow the same general pattern. First, there is a brief general note and frequently some remarks on the epidemiology of the disease. A description of the type of specimens required is given, also the time at which they should be collected for virus isolation, and the methods used in the laboratory. This is followed by instructions for the collection of sera for antibody estimations, the tests used and the interpretation of the results.

Investigation of virus disease in the laboratory is still somewhat specialized work, but this book should be of considerable value to the pathologist who wishes to start work in this field himself, and, what is more important to all concerned, it should aid the physician to obtain the correct material at the correct time for suitable investigation.

The material is clearly laid out and there are numerous useful tables and graphs. Each chapter contains an adequate bibliography up to 1947 or 1948. It is unfortunate that this book, and others of its kind, should be so expensive.

F. O. MacCallum

1601 Oral Vaccines and Immunization by Other Unusual Routes

David Thomson & Robert Thomson, assisted by *James Todd Morrison*. Edinburgh: E. & S. Livingstone Ltd., published for the Pickett-Thomson Research Laboratory, 1948. xi + 329 pages. 28 × 22 cm. £2 2s. [£2.1]

Part I. Oral immunization, general information. (i) Introductory; (ii) historical; (iii) histology of the digestive tract and the mechanism of absorption; (iv) the phenomenon of enterotropism; (v) the protective defences of the digestive tract against the oral invasion of living bacteria; (vi) experimental evidence regarding the permeability of the intestinal mucosa to living bacteria; (vii) methods of increasing the permeability of the intestinal mucosa to bacteria and bacterial toxins; (viii) are bacterial vaccines and toxins given by the mouth altered by the gastro-intestinal secretions as to become useless for immunization purposes? (ix) theories on the mechanism of the immunity induced by oral vaccines. Part II. Oral method of prophylactic immunization against various diseases. (x) Typhoid fever; (xi) bacillary dysentery; (xii) cholera; (xiii) plague; (xiv) tuberculosis; (xv) diphtheria; (xvi) Malta fever; (xvii) oral immunization against pneumococci; (xviii) oral immunization against colds and influenza; (xix) oral staphylococcal vaccines; (xx) oral gonococcal vaccines; (xxi) oral *B. coli* vaccines; (xxii) oral streptococcal vaccines; (xxiii) oral vaccines against Salmonella infections; (xxiv) autogenous oral faecal vaccines in treatment of intestinal infections; (xxv) *Bacillus pyocyaneus* vaccines given per rectum; (xxvi) oral vaccines against animal diseases; (xxvii) oral prophylactic immunization against smallpox; (xxviii) oral immunization against measles with placental extracts; (xxix) passive immunization by seroplasma administered by mouth; (xxx) oral pus vaccines in treatment of septic wounds; (xxxi) oral immunization in hay fever and ragweed pollinosis; (xxxii) oral immunization against poison ivy dermatitis. Part III. Oral prophylaxis with toxins and toxin-antitoxin mixtures. (xxxiii) Scarlet fever; (xxxiv) diphtheria (prophylactic immunization against diphtheria with toxin-antitoxin mixtures by the mouth); (xxxv) staphylococcus toxin; (xxxvi) oral tetanus toxin, etc.; (xxxvii) animal experiments with *Clostridium botulinum* toxin; (xxxviii) oral immunization against serpents' venom; (xxxix) treatment of diphtheria by oral administration of diphtheria antitoxin. Part IV. Immunization by other unusual routes. (xl) Immunization by the respiratory tract; (xli) regional vaccination at the portal of entry; (xlii) treatment and prevention of pyorrhoea by submucous injections and by tooth paste vaccines; (xliii) immunization through the skin by means of ointment vaccines; (xliv) diphtheria prophylaxis by cutaneous inunction; (xlv) tuberculosis treatment by cutaneous inunction with tuberculin; (xlvi) attempts to immunize by installation into the conjunctival sac. References to literature. Index of authors quoted. Index of subjects.

As the authors state in the preface, "This book is an attempt to bring together into one volume the results of many researches on oral vaccines and attempts at immunization by other non-parenteral routes." They have succeeded in compiling a well-documented work of reference which will be of considerable value to those interested in the research aspects of immunization by non-parenteral routes and in their practical application in preventive medicine.

It is agreed that gastric acidity plays an important part as a bactericidal line of defence against orally ingested living bacteria. There is also no doubt about the permeability or penetrability of the intestinal mucosa by certain living organisms—tubercle bacillus, typhoid and paratyphoid bacilli, and Salmonella and Brucella organisms—but how much of this is due to damage to the intestinal mucosa caused by the organisms themselves, or to entry via minor abrasions of the mucosa, is not proven.

It is claimed that bacteria are constantly invading the intestinal mucosa. In dysentery, however, where infection is usually confined to the mucous membrane of the gut but accompanied by ulceration, serum antibody production is very weak; moreover, there is little or no evidence of concurrent antibody formation vis-à-vis the normal flora which might be expected to pass the damaged mucosa.

One-third of the volume is devoted to oral immunization against tuberculosis, especially with living BCG vaccine. The majority of investigators agree that oral BCG does produce immunity, but only after a long interval, and the percentage of positive tuberculin reactors following immunization is not as high as expected. Despite the pioneer work of Calmette and many others, there is now a definite swing from the oral route to the intracutaneous method of administration of BCG.

Prophylactic immunization against typhoid fever by oral vaccines provides the most conclusive evidence of immunity induced by this route. On balance the degree of immunization produced appears at best to be as good as, but in general of a lower order than, that produced by immunization by the usual parenteral routes. There is much less certainty that a satisfactory level of immunity will be produced by the oral route.

Oral vaccines of dysentery (Shiga and Flexner), cholera, and plague organisms have given either inconclusive or disappointing results. Vaccines of dysentery organisms appear to produce a local cellular immunity with little evidence of humoral immunity. No evidence of value in human immunization is adduced for oral vaccines prepared from staphylococci, gonococci, streptococci, Salmonellae or *B. coli*.

A section is devoted to oral immunization against colds and influenza, but these are virus infections, and oral vaccines made from pathogenic and suspected pathogenic respiratory organisms could not be expected to induce immunity, except possibly to secondary invaders. Claims to prevent colds and influenza by the use of bacterial vaccines given orally (or parenterally) must be

viewed very critically and the evidence brought forward provides little support for their value.

Reference is made to investigations as to the value of vaccines administered by inhalation, intratracheally, intranasally, spraying into the nose and throat, incorporated in toothpastes, in ointments for skin inunction, and via the rectum and conjunctiva. There does not appear to be much future for these routes except perhaps by skin inunction, and the immunity produced is slow to develop and not so potent as that produced by injection methods.

In fine, oral vaccines appear to be subject to wide variation in the absorptive powers of the intestinal mucosa in different individuals; much larger doses are required—40 to 100 times greater than those given by the usual parenteral routes; antibodies are slow to develop, and the level of immunity produced does not appear in general to be as high as that introduced by immunization by skin injection methods. On the credit side, there is the ease of administration, repeated as often as may be desired, and the almost total absence of reactions.

V. D. Allison

1602 The Filterable Viruses

Francis O. Holmes. London: Baillière, Tindall & Cox, 1948. (Supplement No. 2, Bergey's Manual of Determinative Bacteriology, Edition VI, 1948.) 160 + xxiii pages. 23 × 15 cm. £1

The classification of bacteria has long been a matter for disagreement. Undoubtedly we shall eventually attain the ideal of a comprehensive classification using the binominal system of nomenclature but it is impossible simply to adopt the rules which have been found applicable to the taxonomy of animals and plants. Ambitious schemes have been suggested, notably by Bergey and his collaborators, and their system is expounded in the well-known *Manual of determinative bacteriology*. However, their classification has not received any general assent because many feel that the criteria used to define species are too unstable to be of a taxonomic significance and that the time is not yet ripe for any detailed system because of the peculiar way in which bacteriology has been studied, i.e., mainly as an applied medical science. The study of viruses is even more in its infancy, and to attempt any classification at this stage is a most hazardous undertaking. This supplement to Bergey's *Manual*, however, represents such an attempt.

While the reviewer is not competent to criticize the treatment of the plant viruses, he must state his opinion that the classification of the animal viruses and of the bacteriophages is far from satisfactory. The suggested classification of the bacteriophages is useless for all practical purposes and adopts an extremely limited view of even our present knowledge of these ubiquitous viruses. The classification of the animal viruses is somewhat of a travesty. It is possible to mention here only a few examples to illustrate the curiosities which abound.

There is no agreement that the common-cold virus has ever been isolated, yet it is here classified as *Tarpeia premens* (from Tarpeia, name of a Roman maiden who treacherously opened a citadel to an enemy). In contrast, there are many well-recognized viruses, such as Horsfall's mouse pneumonia virus, which are not mentioned at all. There is no recognition of the fact that the ectromelia virus is closely related to the pox group. The mumps virus is classified for no good reason with the animal salivary gland viruses, but its relationship to the viruses which cause haemagglutination is disregarded. The urgent practical problem of discovering the relationships between the poliomyelitis viruses, Theiler's O virus, the S.F. groups, and the M.M. group, is not considered.

The new names proposed have nothing to recommend them except their unfamiliarity and their elusive classical connotations. In bacteriology it has happened that elaborate systems of classification of certain groups of which we have special knowledge, such as the Salmonellae, have received wide agreement. In the same way tentative schemes for the classification of the influenza viruses have begun to appear. And it is better that taxonomy should proceed for a time in this piece-meal fashion.

It is to be earnestly hoped that at the next International Microbiological Congress the present proposal will be repudiated and that the attempt to classify viruses will be postponed until more is known of this subject.

Forrest Fulton

1603 Haemoglobin: A Symposium Based on a Conference Held at Cambridge in June 1948 in Memory of Sir Joseph Barcroft

Edited by *F. J. W. Roughton & J. C. Kendrew.* London: Butterworth's Scientific Publications, 1949. xii + 317 pages; illustrations. 25 × 16 cm. £2

(i) Tributes to Sir Joseph Barcroft; (ii) reversible reactions with oxygen and carbon monoxide; (iii) analysis and amino acid composition; (iv) X-ray crystallography; (v) physico-chemical properties; (vi) biochemical and physiological aspects; (vii) differences between adult and foetal haemoglobin; (viii) comparative biochemistry and physiology of oxygen carriers. Author index.

This is a memorial volume to Sir Joseph Barcroft, who died in March 1947. It contains contributions of those who were invited from all parts of the world to attend a symposium on haemoglobin. The symposium was held in Cambridge in June 1948 in commemoration of Barcroft, to whose classical work is owed so much of the knowledge of the respiratory function of blood. The symposium was also held to carry on the annual meetings to discuss problems related to haemoglobin that Barcroft inaugurated in Cambridge after the war.

The book illustrates how biological science makes use of every available tool of the physical sciences. Thus there are contributions from physical chemistry, organic chemistry, spectroscopy, crystallography and mathematical physics; this makes the book of great interest to chemists, as well as to physiologists and biochemists.

The first of the book's eight sections contains tributes by eight physiologists who knew and worked with Barcroft. They give a vivid and delightful insight into his personality and greatness, each revealing a different facet of his quality. Each of the sections following contains original papers by different authors, giving their context, and can thus be appraised by anyone unfamiliar with the field. The work described is outstanding; the papers are stimulating and readable. The majority deal with experimental work, but some are entirely given to theoretical discussion. For example, Wyman discusses the relation of the kinetic data of the reactions of haemoglobin to the shape of the molecule (for a fuller account see *Advances in Protein Chemistry*, vol. 4), and Pauling discusses its electronic structure in relation to its properties.

The papers are not well arranged, however, and this gives a disjointed impression. It would have been more logical to place Roughton's gasometric determinations of oxygen dissociation curves, and their relation to the intermediate-compound hypothesis, before Drabkin's latest elegant spectrophotometric measurements in vivo. The latter do not coincide with gasometric measurements, the validity of which when applied to the living animal is questioned. The arrangement of the crystallographic section can also be criticized. Here a simplified explanation of mathematical methods used in crystallography appears at the end. Anyone but a crystallographer would find it helpful to read this before the other papers, which include brilliant analyses of horse haemoglobin and myoglobin, in which the shapes of the molecules are deduced in remarkable detail.

Lack of space prevents even a cursory indication of the most interesting papers, which include an account of a new method of determining "end-groups" in proteins. Apart from a small section on cytochrome C, the book is concerned only with haemproteins functioning as oxygen carriers, and furthermore embraces an interesting comparison of the oxygenation efficiency of haemoglobin and haemocyanin, whose prosthetic group is not a porphyrin. Most of the work described was unpublished at the time of the conference, and so the book is up to date.

H. M. Muir

1604 Cardiovascular Studies

Kenneth J. Franklin. Oxford: Blackwell Scientific Publications, 1948. xvi + 306 pages; 102 figures. 25 × 19 cm. £2 2s. [£2.1]

Part I. Historical note on the Eustachian valve and the intervenous tubercle of Lower. Part II. (i) Terminology; (ii) techniques, and the evolution of a concept; (iii) note-taking; (iv) some general references to the literature, and an introduction to personal observations; (v) *Homo sapiens*. References to the literature, personal observations, and Table I. Part III. References to the literature, and personal observations on other mammals. (i) Primates; (ii) Menotyphla; (iii) Lipotyphla; (iv) Chrysochloridea; (v) Dermoptera; (vi) Chiroptera; (vii) Carnivora (Carnivora vera, or Fissipedia); (viii) Pinnipedia; (ix) Cetacea; (x) Rodentia (or Rodentia simplicidentata); (xi) Lagomorpha (or Rodentia duplicidentata); (xii) Proboscidea; (xiii) Hyracoidea; (xiv) Perissodactyla;

(xv) Artiodactyla; (xvi) Sirenia; (xvii) Tubulidentata; (xviii) Pholidota; (xix) Xenarthra; (xx) Marsupialia; (xxi) Monotremata. Table II. Part IV. Concluding remarks. Bibliography. Index.

This book provides evidence for the author's concept that the presence, height, and disposition of the eustachian valve are related to the direction of flow of the (right) anterior caval blood stream into, and across, the right atrium of the mammalian heart. The evidence given is derived from anatomical dissections of more than 200 specimens representing every order of the mammalia, as well as physiological observations based on the examination of cine-radiographic records.

Lest such a summary, however, should suggest that the book is of limited appeal and of use to a small number of specialists only, let it be said that this is far from the case. Among many interesting sidelights Dr Franklin explains why he finds a careful study of the literature of his subject, even though it may have covered several centuries, of importance in his current research work. Anatomists and experimental embryologists will appreciate his demonstration of the way in which advances in anatomical knowledge result from investigations based on physiological directives. They will also be grateful for a valuable collection of comparative anatomical data on the mammalian heart. Physiologists, on the other hand, will be particularly interested in the book as a noteworthy contribution to the subject of haemodynamics.

Finally, the ordinary reader also will enjoy the book, for he will see in it the aspirations and difficulties of the medical research worker, and will, moreover, be delighted both by the scholarly manner in which the author approaches his subject and by the narrative style and autobiographical details which add to the interest of this sound scientific monograph.

G. Weddell

1605 Bases Electrophysiologiques de l'Electrocardiographie : ses Applications Cliniques

Enrique Cabrera. Paris : Masson & Cie, 1948. 209 pages ; 90 figures. 25 × 17 cm. 930 fr.

(i) Introduction et théories électrocardiographiques ; (ii) les vecteurs cardiaques ; (iii) les ondes électrocardiographiques ; (iv) le gradient ventriculaire ; (v) les hypertrophies auriculaires et ventriculaires ; (vi) les blocs de branche ; (vii) les syndromes d'insuffisance coronarienne. Index.

In recent years a number of authors have attempted to explain the relationship between the electrocardiogram and the events in the heart producing it. For the clinical cardiologist these explanations have been of particular value when they have helped him to distinguish changes due to the position of the heart from those due to cardiac disease, and so to allow for the former in interpreting the latter. It is unfortunate that this has usually been done in terms of the so-called unipolar limb leads, for clinicians will regard them with justifiable suspicion until they are as well known empirically as the standard leads.

In *Bases électrophysiologiques de l'électrocardiographie* Enrique Cabrera avoids this difficulty by an approach to the problem from a different angle. He explains clearly and simply how the instantaneous potential vector is derivable, by a dipole method, from a knowledge of the extent of depolarization of the septal, endocardial and epicardial surfaces of the heart at any instant during the cardiac cycle. The temporal sequence of depolarization is thus seen to give rise to a vector, the amplitude and direction of which are varying throughout the cardiac cycle. The potentials recorded with the standard limb leads, or indeed with any lead, are the projections of this vector on the " axis " of the lead, but the relation of the " axis " to the geometrical line joining the electrodes is not discussed.

The normal vector cardiogram is seen to be an ovoid, the plane projection of which is commonly a " figure of 8 " pattern, the orientation of which varies over a stated range, but the general shape does not vary significantly. In disease, both orientation and shape may be abnormal, and the major part of this volume is devoted to these changes in the electrocardiogram.

There should be no difficulty in reading and understanding this work for anyone with a smattering of French, for the author's easy style overcomes all the inherent difficulties of the subject. The same high standard is attained in the diagrams. The presentation is of necessity didactic, and alternative theories, although sometimes acknowledged, are not discussed at length.

The book can be recommended without reserve to all interested in the interpretation of the electrocardiogram.

W. F. F. & M. P. S.

1606 Photoelectric Methods in Clinical Biochemistry

G. E. Delory. London : Hilger & Watts Ltd., 1949. x + 90 pages ; 21 figures. 23 × 14 cm. 15s. [£0.75]

(i) The principles of colorimetry ; (ii) colorimetric measurements ; (iii) special technique of photoelectric colorimetry ; (iv) the Spekker photoelectric absorptiometer ; (v) the Biochem absorptiometer ; (vi) recommended analytical procedures. Appendix. Author index and bibliography. Subject index.

This is essentially a book of recipes giving details for the estimation of all the constituents in blood and urine that are of importance in clinical biochemistry. All the estimations described are colorimetric, for this book is designed especially for use with two instruments manufactured by Messrs Hilger & Watts Ltd.—the Spekker absorptiometer and the simpler Biochem absorptiometer. The correct use of these two instruments is described in detail, while the general principles of colorimetry, including the theoretical aspects, are adequately dealt with in the first three chapters.

Users of the two instruments concerned, and of the several other similar instruments which are at present on the market, will find this book valuable on account of its wealth of practical detail, even though they may use photoelectric colorimeters for purposes other than those of clinical biochemistry, while the clinical biochemists will find here a valuable collection of reliable methods.

The analytical procedures described have all been published elsewhere and are essentially those which have been popularized by Professor E. J. King of the Postgraduate Medical School of London ; it is satisfactory to note that they include the estimation of haemoglobin in blood and of 17-ketosteroids in urine. The book is written simply and clearly and contains a wealth of useful information in its 90 pages. It should find a wide popularity in clinical laboratories.

J. N. Davidson

1607 Iron Metabolism and its Clinical Significance

A. Vannotti & A. Delachaux. London : Frederick Muller Ltd., 1949. 267 pages. 25 × 16 cm. £1 12s. [£1.6]

Part I. The biological significance and normal metabolism of iron. (i) General biological considerations regarding the physico-chemical properties of iron ; (ii) the metabolism of iron ; (iii) the biological significance of iron ; (iv) the circulating iron ; (v) considerations regarding the physiology of non-haemoglobin iron. Part II. Iron metabolism under pathological conditions. (i) Iron and blood changes ; (ii) iron and the reticulo-endothelial system ; (iii) iron metabolism in lead poisoning ; (iv) iron and the hyperfunction of the bone marrow ; (v) iron in hepatic diseases ; (vi) iron and general metabolic disturbances ; (vii) general conclusions. Part III. Clinical indications and practical considerations in iron therapy. (i) The most important iron preparations ; (ii) the use of iron therapy ; (iii) contra-indications of iron treatment ; (iv) the doses and duration of iron therapy. Bibliography. Subject index. Author index.

The authors give a very full review of the experimental work in the field of iron metabolism, including that with radioactive iron. They outline their own experiments, which lead them to stress the part played by iron as a catalyst in a number of biochemical processes and its part in tissue oxidation. Their division of non-haemoglobin iron into four fractions and the variations in these fractions under certain physiological and pathological conditions is interesting, but diagnostically and therapeutically does not seem to have made much advance on the old classification of " easily split-off iron". The bibliography is excellent, and for the expert in the field this book should prove stimulating.

M. E. Morgans

1608 Documenta Ophthalmologica. Advances in Ophthalmology. Vol. III

Edited by *F. P. Fischer, A. J. Schaeffer & Arnold Sorsby.* The Hague : Dr. W. Junk, 1949. 328 pages ; illustrations. 24 × 16 cm.

(i) Selig Hecht, an appreciation ; (ii) the present status of the trichromatic theory ; (iii) retinal structure and colour vision ; (iv) the laminar pattern of the lateral geniculate nucleus considered in relation to colour vision ; (v) the analysis of retinal elements by the micro-electrode technique ; (vi) the photochemistry of vision ; (vii) increment thresholds and the mechanisms of colour vision ; (viii) the polychromatic theory ; (ix) colour vision in the central fovea ; (x) colour discrimination and the influence of colour contrast on acuity ; (xi) colour recognition of very small light sources ; (xii) current views on colour blindness ; (xiii) brightness, visual acuity and colour blindness ; (xiv) some aspects of anomalous vision ; (xv) phenomena observed in veiled colours ; (xvi) chromatic aberration of the eye ; (xvii) the two-quanta explanation of the dependence of the threshold values on the visual angle and the time of observation.

This book must be unique in having contributions, representing attacks on a common fundamental problem, from physicists, physiologists, anatomists, histologists, photochemists, and psychologists. Neuro-anatomy, the quantum theory and non-Euclidean

geometry are all involved. It is difficult therefore for the reviewer to do justice to the variety of material; to be equally happy with the descriptive anatomy of the micro-structure of the retina, the terminology used in colour psychology and with the mathematics of highly contorted surfaces. If, however, he cannot express an expert opinion on each and all of the papers, he can at least be thankful that the bad old days of acrimonious debate between protagonists of different colour vision theories conceived from physical, psychological, comparative anatomical, physiological or evolutionary standpoints, have given way to a state of affairs where the bulk of the interested parties from a large part of the world can gather together and genuinely begin to understand each other's language and approach. Let us hope that this will be the first of many similar conferences.

It is a pity, in view of the particular nature of the compilation, that the discussions are not more fully reported. One gets a few accounts of the cross-questioning of, for example, a physiologist by a physicist; but more might have been included. There are some glaring examples of faulty logic (dare I say, more particularly on the part of biologists ?). Polyak in his paper on the structure of the retina concludes (p. 31) that because the central foveal cones are morphologically fairly uniform, they must all be alike in photochemical properties. Again, he concludes (p. 43) that because there is colour vision in the central fovea, an area he declares to be rod-free, " . . . this rules out the rods from the rank of mechanisms instrumental in colour vision in the strict sense." Hartridge and Granit, both physiologists, appear to have come in for the heaviest fire of criticism. It is difficult to avoid the impression that the former, in spite of a fine collection of references, has not understood them all, or at least is not accurately representing the arguments of others, while the latter offsets brilliant experimental ability with a lack of critical appraisal in presenting his results and conclusions.

Altogether this is a most stimulating book, of no narrow interest, not only to researchers on colour vision, but to neurologists, experimental psychologists, biophysicists and many others. It is handsomely produced and typographical errors are few. To have included an index would have been rather a luxury. If there is any complaint about the production it is that a better type face might have been chosen for a book on vision. One is surprised also to find no mention of the contents of the preceding volumes, I and II in the Advances in Ophthalmology series.

H. V. W.

1609 Visual Development. Vol. 1

J. H. Prince. Edinburgh: E. & S. Livingstone Ltd., 1949. xii + 418 pages; 190 figures. 22 × 14 cm. £2 10s. [£2.5]

Part I. (i) Photoreception; (ii) perception; (iii) retinal structure in man; (iv) retinal structure in animals; (v) photochemical aspects; (vi) retinal stimulation quanta. Part II. (vii) Evolution (invertebrate); (viii) evolution (vertebrate); (ix) the evolution of nocturnality and the return to diurnality; (x) pupillary function; (xi) increased sensitivity of the retinal bacillary layer; (xii) tapeta; (xiii) sightless vertebrates and luminous organs. Part III. (xiv) Colour appreciation in the lower orders; (xv) evolution of colour vision; (xvi) colour vision in man. Part IV. (xvii) Night-vision and dark-adaptation in man; (xviii) night-vision and dark-adaptation tests; (xix) the association of nystagmus with retinal defects. Part V. (xx) Routine examination of the eyes of animals; (xxi) examination of sections through the microscope; (xxii) fundus significance. Glossary. Bibliography. Index.

As we look into the outside world, we are conscious of the shapes and sizes of external objects; we perceive their colour, their solidity and their form; we can estimate their distance from us; we can discern their movement, or we can observe our own movement with respect to these objects; moreover, we can perform many of these feats over a very wide range of illumination, and we can carry away mental pictures of all that we have seen.

When we study our own eyes, we can to some extent correlate structure with function; and when we study the eyes of animals we see other patterns and other arrangements correlated with the same and other functions. By comparative methods a fuller understanding is obtained, and in no subject is this more true than in vision, for the field of vision has indeed many sides. Important contributions to the growth of knowledge in that field have come, and must come again, from physicists, physiologists, psychologists, physical chemists, zoologists and naturalists.

When the breadth of the subject is thus considered, it is clear that the author of *Visual development* has set himself a large task and has thus of necessity laid himself open to much criticism, since it is hardly possible to be equally expert in all branches. Nevertheless, in this first volume, he brings together much important information and compels the student of vision to think beyond the range of purely human sight. It is with the help of contributions of this type that the human eye can be seen in its true relationship as a single point in the evolutionary development of the eye in general, with some advantages over other eyes and with some disadvantages.

The book is divided into five parts. In Part I, the general functions of the eye are discussed and the salient features of retinal structure and cerebral representation in man and animals are described. This part, like so many earlier discussions of the subject, suffers from some confusion of thought, much of which arises out of the definition or lack of definition of the terms " rod " and " cone ". Moreover the illustrations in this part of the book do not assist as much as they might.

Part II is devoted first to the evolution of eyes in both invertebrates and vertebrates, and this is followed by a discussion of eyes in relation to diurnal and nocturnal activity, with particular reference to such things as pupil shape, retinal structure and the formation of tapeta. In much of this section attention has been diverted to aspects of evolution other than those concerned directly with vision. Sometimes this is helpful, but often it borders on the irrelevant. Nevertheless it is clearly an important approach to a proper understanding of vision to relate the evolution of the optical structure to the evolution of the animal's structure and behaviour as a whole.

Part III discusses the significance of colours and colour vision, and gives an account of the occurrence and possible significance of colour vision in different groups. Some of the chief theories of human colour vision are also discussed. In Part IV, an account of dark-adaptation and its measurement, and of the relationship of nystagmus with night vision, is given. Part V jumps surprisingly from a description of how to hold live snakes to a practical guide to the preparation of eyes for routine histological examination, and thence to a descriptive account of the structure of the fundus of a wide variety of eyes.

The volume as a whole contains much interesting, and often unusual and important, information, but it is somewhat uncritical in outlook and devotes, at times, far too much space to matters which seem beyond its proper domain.

E. N. Willmer

1610 Pathology

Edited by *W. A. D. Anderson.* London: Henry Kimpton, 1948. xii + 1453 pages; 1183 illustrations; 10 colour plates. 25 × 17 cm. £3 15s. [£3.75]

(i) Introduction; (ii) cells and their behavior; (iii) inflammation; (iv) degenerative changes and disturbances of metabolism; (v) disturbances of circulation; (vi) physical agents in the causation of injury and disease; (vii) chemical injury; (viii) effects of radiation; (ix) general principles of infection and resistance; (x) bacterial diseases; (xi) tuberculosis; (xii) tuberculoid conditions; (xiii) leprosy; (xiv) spirochetal and venereal diseases; (xv) rickettsial and viral diseases; (xvi) fungus infections; (xvii) protozoal and helminthic infections; (xviii) vitamins and deficiency diseases; (xix) neoplasms; (xx) the heart; (xxi) the blood and lymphatic vessels; (xxii) the kidneys; (xxiii) the lower urinary tract and male genitalia; (xxiv) the lung; (xxv) the organs of special senses; (xxvi) the lips, mouth, teeth, and neck; (xxvii) the gastrointestinal tract; (xxviii) the liver; (xxix) the gall bladder and bile ducts; (xxx) the pancreas; (xxxi) diabetes mellitus; (xxxii) the blood and bone marrow; (xxxiii) the spleen, lymph nodes, and reticulo-endothelial system; (xxxiv) the thymus; (xxxv) the pituitary gland (hypophysis); (xxxvi) the pineal; (xxxvii) the thyroid; (xxxviii) the parathyroids; (xxxix) the adrenals; (xl) the female genitalia; (xli) the breast; (xlii) the skin; (xliii) the bones; (xliv) the joints; (xlv) the nervous system; (xlvi) heredity and constitution in disease. Index.

This book is the result of the successful collaboration of 32 American pathologists, who represent 18 of the 48 United States of America. It weighs seven pounds, has 46 chapters, 1453 pages and 1183 illustrations. An almost staggering amount of detailed pathological information has been compressed between its covers, largely by the liberal use of small type. The illustrations, with few exceptions, are of good standard; an appreciable number is excellent.

Approximately one-third of the book deals with general pathology and in this section there are excellent chapters on chemical and physical injury and the effects of irradiation. The detailed treatment of the latter subject is fully justified by the widespread use of therapeutic irradiation, and the large amount of information presented could otherwise be obtained only by reference to special articles. The effects of atomic bomb injury are described. There is a clearly written and well-illustrated account entitled " Vitamins and deficiency diseases," by Henry Pinkerton. More

than one-fifth of the book deals with specific infections and there are special chapters on protozoal and helminth infections which, it is claimed, should now be included in any pathological textbook in view of the rapid progress of world-wide travel. Included also in the section on general pathology are several short chapters which introduce the student to major pathological problems. These are without exception clearly and carefully written. E. V. Cowdry's chapter on cells and their behaviour is stimulating and original. Paul R. Cannon writes a terse introduction of a few pages to the general problems of infection and resistance, and the introductory account of the general pathology of tumours by Shields Warren is one of the best in the book. There is an admirable chapter on the general pathology of tuberculosis by Francis D. Gunn.

Many of the sections dealing with special pathology are almost monographic. Ernest M. Hall's chapter on the special pathology of the heart occupies 70 pages and contains 309 references. The endocrine system is dealt with by the editor, W. A. D. Anderson, in six chapters occupying 88 pages and giving 507 references. Diseases of the blood and lymphatic vessels, the kidneys, the lung and liver are afforded the same almost encyclopaedic treatment. A commendable feature of the book is the special consideration given to diseases of the ear, nose, throat, and eye, of the skeletal tissues, the skin and the nervous system. It is claimed that these branches of pathology have previously received insufficient consideration in textbooks and there is obviously every justification for their inclusion in a book of this size. There is no doubt that these chapters add materially to the value of the book as a work of reference.

In almost all chapters considerable emphasis is laid on structural changes, but outstanding clinical features and the morbid physiology of disease receive attention, and neither bacteriology nor immunology are neglected. In some instances the correlation between altered structure and abnormal function could have been extended. There is a brief account of the consequences of abnormal function in liver disease but no corresponding general introduction to renal efficiency and failure in the chapter on the kidney. A short chapter on the functional efficiency of organs and the general principles of its estimation might well be included in the general pathology section. The descriptions of some common diseases, peptic ulcer for instance, are too brief having regard to their clinical importance, and it might be advantageous if a short general introduction to the reticulo-endothelial system were included in the earlier part of the book. This would provide the student with a demonstration of the part played by experimental pathology in the evolution of the subject.

There is no question that this book will take its place as an important contribution to pathological literature. Most of the earlier chapters on general pathology, especially the excellent account of inflammation by Morton McCutcheon, could be read with profit by the undergraduate medical student, but the chapters on special pathology are far too detailed for undergraduate study. To pathologists and clinicians it will prove to be an exceptionally useful reference book, especially with regard to recently acquired pathological knowledge.

G. Hadfield

1611 Textbook of Bacteriology. (Eleventh Edition of Muir & Ritchie's "Manual")

C. H. Browning & T. J. Mackie. Eleventh edition. London: Geoffrey Cumberlege, Oxford University Press, 1949. x + 907 pages; 226 figures. 25 × 16 cm. £2 10s. [£2.5]

(i) General morphology and physiology of bacteria; (ii) relations of bacteria to disease—infection—production of toxins by bacteria; (iii) immunity; (iv) bacteria associated with acute inflammation and suppuration—staphylococci and related organisms: streptococci; (v) the pneumococcus (*Diplococcus pneumoniae*); (vi) the meningococcus and gonococcus and allied organisms (Neisseriae); (vii) the diphtheria bacillus and allied organisms (Corynebacteria); (viii) the tubercle bacillus and the commensal and saprophytic acid-fast bacilli (Mycobacteria); (ix) the leprosy bacillus: bacillus of Johne's disease; (x) the anthrax bacillus; (xi) the bacilli of glanders and melioidosis; (xii) bacillus pyocyaneus, bacillus proteus, and bacillus faecalis alkaligenes; (xiii) the coliform bacilli and the pneumobacillus; (xiv) the enteric group (the typhoid bacillus and the paratyphoid bacilli) and the Salmonella group of food-poisoning organisms; (xv) the dysentery bacilli and allied organisms; (xvi) the bacillus of plague and allied organisms (Pasteurella group); (xvii) the organisms of undulant fever and epizootic abortion (Brucella group); (xviii) the influenza bacillus, bacillus pertussis, and allied organisms; (xix) the cholera vibrio and allied organisms; (xx) the sporing anaerobic bacilli (Clostridia); (xxi) actinomyces and allied organisms; (xxii) bacillus (or actinomyces) necrophorus: bacteroides: bacillus fusiformis: bacterium pneumosintes: streptobacillus moniliformis: bacterium monocytogenes: erysipelothrix: organism of bovine pleuropneumonia and allied organisms: bacterium tularense; (xxiii) *Treponema pallidum* and *Treponema pertenue*; (xxiv) spirochaetes of the relapsing fevers (*Borrelia obermeieri* or *recurrentis*; *Borrelia duttoni*, etc.): *Borrelia vincenti*; (xxv) *Leptospira icterohaemorrhagiae*, etc.: *Spirillum minus*; (xxvi) the rickettsiae of typhus fever, etc.: Bartonella; (xxvii) viruses in general: neurotropic viruses—rabies, etc.: epidemic poliomyelitis: encephalitis of man and animals: lymphocytic choriomeningitis, etc.; (xxviii) dermotrophic viruses—smallpox and vaccinia, etc.: foot and mouth disease: herpes zoster: chickenpox: herpes simplex: molluscum contagiosum: warts; (xxix) viruses (*continued*)—yellow fever: Rift Valley fever: infective hepatitis and homologous serum jaundice: dengue: phlebotomous fever: psittacosis, etc.: lymphopathia venereum (lymphogranuloma inguinale): trachoma: inclusion conjunctivitis; (xxx) viruses (*continued*)—epidemic influenza, etc.: infectious coryza: virus pneumonia: measles: rubella: Durand's disease: infective mononucleosis: mumps: epidemic kerato-conjunctivitis: epidemic gastroenteritis: canine distemper: rinderpest: swine fever: virus myocarditis: infectious neoplasms of rabbits: virus diseases of domestic birds; (xxxi) bacteriophage; (xxxii) the pathogenic fungi; (xxxiii) pathogenic protozoa—malaria plasmodia: babesia (piroplasma): theileria; (xxxiv) pathogenic protozoa (*continued*)—entamoeba histolytica and commensal amoebae: flagellates of the alimentary and genito-urinary tracts: balantidium coli; (xxxv) pathogenic protozoa (*continued*)—trypanosomes (*T. gambiense*: *T. rhodesiense*: *T. cruzi*: animal trypanosomes); (xxxvi) pathogenic protozoa (*continued*)—leishmania: toxoplasma; (xxxvii) chemotherapy; (xxxviii) the bacterial flora of the normal skin and mucous membranes; (xxxix) the bacteriology of air, water, sewage, soil, and milk, from the hygienic standpoint. Appendix. Bibliography. Index.

"Muir & Ritchie" was first published 53 years ago, and many bacteriologists and others who began their studies with it will be glad that this outstanding textbook is being maintained. It now appears in a new format, the larger page and the use of small type for subsidiary matter enabling the subject to be treated as fully as in earlier editions, although the bulk of knowledge to be presented has, of course, greatly expanded. The authors have been successful in preserving the style of the original in adding to, or re-writing, the text.

The latter part of the book includes a full account of viruses, a chapter on the pathogenic fungi by R. Cranston Low, and four chapters on protozoology—exceptionally thorough treatment of this subject in such a work. There are, also, chapters on chemotherapy, the normal flora of the body, the bacteriology of air, water, sewage, soil, and milk, and a full appendix on methods. Finally, there is a classified bibliography of no less than 54 pages; this is so extensive that the average student may well recoil from it, and some of the citations, going back well into the last century, are of little more than historical interest.

The feature most likely to attract criticism is the use of the terminology of previous editions, in which, for instance, the generic name for every rod-shaped organism is "bacillus." In headings of sections dealing with specific bacteria modern equivalents are given only in brackets after the old nomenclature. Admittedly the new terminology is not even yet universally agreed or accepted, but surely the time has come when the well-recognized, more descriptive modern generic names should be used by every author. Their use is now required by the editors of almost every journal of standing published in the English language, and if in Britain we have not all yet gone so far as to adopt *Escherichia* and *Eberthella*, everyone knows what is meant when *Bacterium* and *Salmonella* are used instead. Other, though less important, features of previous editions of the book, the inclusion of which might well be reconsidered in the next edition, are occasional descriptions of named bacteria with uncertain claims to recognition as distinct species, and discussions of the value of vaccine treatment for various infections—the fact that after so many years the verdict often remains inconclusive or frankly sceptical surely suggests that some of these methods had better be forgotten. The description of antibiotics is rather cursory and brief, and it might well have been mentioned in Chapter X that bacilli are the source of many interesting substances of this kind.

The book has many solid merits. It contains far more detailed information than the majority of single-volume works on bacteriology, which should commend it to the more ambitious student who is not content with a book containing only the minimum that he should know. It stands in fact almost alone among British publications, in a position intermediate between the ordinary small textbook and the more encyclopaedic works of reference. It is profusely and, in general, well illustrated; some of the photographs, particularly of bacterial colonies, attain a high degree of excellence. As a source of detailed and accurate information it will be useful in many directions to the professional bacteriologist as well as to the advanced student.

L. P. Garrod

1612 Principles of Human Physiology

Originally written by *E. H. Starling*. Tenth edition by *C. Lovatt Evans*, with chapters on the special senses, by *H. Hartridge*. London: J. & A. Churchill Ltd., 1949. xii + 1193 pages; 693 illustrations. 25 × 16 cm. £2 2s. [£2.1]

(i) Introduction. Book I. General principles. A. Structural principles. (ii) The structural basis of the body. B. Biochemical principles. (iii) The elementary constituents of protoplasm; (iv) the proximate constituents. C. Biophysical principles. (v) The energy of molecules in solution; (vi) the properties of colloids; (vii) the passage of water and solutes through membranes; (viii) bioelectric potentials; (ix) enzymes and enzyme action. Book II. Tissues subserving movement and conduction—muscle and nerve. (x) Voluntary striated muscle; (xi) plain muscle and other contractile tissues; (xii) nerve fibres. Book III. Centralized control and co-ordination—the central nervous system. (xiii) General features of a central nervous system; (xiv) the receptors; (xv) the spinal cord and its relationship to the higher parts of the central nervous system; (xvi) the excitability of neurones and the properties of conduction at synapses; (xvii) characteristics of reflex actions; (xviii) the labyrinth, and postural reflexes; (xix) higher afferent paths; (xx) the cerebral hemispheres and the efferent paths; (xxi) functions of the cerebral cortex; (xxii) the cerebellum; (xxiii) the autonomic system: the hypothalamus: humoral transmission. Book IV. The supplying of information—the special senses. (xxiv) The nervous mechanism of sensation; (xxv) vision; (xxvi) hearing and speech; (xxvii) cutaneous sensations; (xxviii) sensations of smell and taste. Book V. Systems for distribution of materials—blood, circulation and respiration. (xxix) The blood; (xxx) general features of the circulation; (xxxi) physiology of the heart; (xxxii) factors which modify the heart's action; (xxxiii) dynamics of the circulation; (xxxiv) local regulation of blood flow; (xxxv) the pulmonary, hepatic and cerebral circulations; (xxxvi) examples of circulatory adaptation; (xxxvii) lymph, tissue fluids, and cerebro-spinal fluid; (xxxviii) the defence of the organism against infection; (xxxix) respiration; (xl) the regulation of the respiratory movements. Book VI. The intake of materials—nutrition, metabolism. (xli) The exchanges of matter and energy in the body; (xlii) the vitamins; (xliii) the normal diet of man; (xliv) the physiology of digestion—changes undergone by the foodstuffs in the alimentary canal; (xlv) the absorption of the foodstuffs; (xlvi) the history of the foodstuffs. Book VII. The removal of waste material and temperature conservation—excretion and temperature regulation. (xlvii) Renal excretion; (xlviii) the skin and the skin glands; (xlix) the temperature and heat-balance of the body. Book VIII. The provision of special chemical stimulants, and of measures for continuance of the species—the endocrine organs and reproduction. A. Endocrine organs. (l) The endocrine organs. B. Reproduction. (ii) The formation of germ cells; (iii) reproduction in man and other mammals; (liii) the secretion and properties of milk; (liv) heredity. Index.

In 1911 the Sharpey Scholarship at University College was awarded by Professor Ernest Starling to a candidate at the Second Medical Examination who was not a student of the College but an external candidate from Birmingham. The successful scholar was outstanding in his year and within two years was awarded the doctorate in science. He then qualified in medicine and, after a distinguished career in the First World War, progressed via the Chair of Physiology at Leeds, and the National Institute at Hampstead, to the Starling Chair at University College, from which he retired in 1949. With the Chair, Lovatt Evans inherited the principles of Starling in all senses of the word and the high tradition of this well-known book is maintained in this revised edition.

It is distinguished among books because the present author is qualified to speak and write from his personal research experience in both the biochemical and biophysical branches of physiology. In addition to authoritative discussion of the subject, the cultured, and wide but balanced, treatment it receives evinces itself particularly in this edition.

Each section is prefixed by a full and lucid account of the historical evolution of the present position. Collectively, the historical sections would make a co-ordinate history of physiology worthy of publication, as such, alone. In addition, physiology has been interpreted in a very wide sense, in that the ancillary aspects of biology which contribute to human physiology are brought into the picture, notably the basic principles of immunity, morphogenesis and genetics. Where a subject is treated lightly the reader is enabled to delve deeper by using the carefully selected references, both in the footnotes and at the chapter endings—a particularly useful feature of the book.

Probably, however, the most important feature is the excellent and thorough treatment that is given to the modern advances in biochemistry, and particularly the "bio" aspect of that subject, so often slurred over by the biochemist. This could not have been done if Evans' training and research had not been uniformly spread over both the chemical and experimental fields in the living animal or human being, as well as in the test-tube or colorimeter. There probably is no other university teacher living who could do this. The work is extremely up to date and is parallel with the growing points of physiology.

It would be invidious to point out the inaccurate footnote on p. 1135, or to suggest that this or that might be written more fully. The author has provided an up-to-date textbook of convenient size and a sound philosophy of true scientific method. In this, as in previous editions, the aid he has received from Professor Hamilton Hartridge, in the latter's own field of the special senses, adds lustre to the book. The gift possessed by this collaborator in describing the complex in simple words is well exhibited in this section.

This standard book is still pre-eminent as a scientific guide to human medicine. May it long remain so.

A. St.G. Huggett

1613 La Streptomycine

Marcel Morin, Jaques Nehlil & Rémy Pichon. Paris: Masson et Cie, 1949. viii + 509 pages; 49 figures. 25 × 17 cm. 1950 fr.

Part I. (i) Historique; (ii) production; (iii) propriétés générales; (iv) récupération dans les urines; (v) autres substances antibiotiques élaborées par *Streptomyces griseus*; (vi) titrage de la streptomycine; (vii) action "in vitro"; (viii) traversée dans l'organisme. Absorption. Diffusion. Elimination; (ix) mode d'emploi; (x) toxicité; (xi) résistance secondaire à la streptomycine. Part II. (i) La streptomycine dans les infections liées aux bactéries hémophiles; (ii) la streptomycine dans les infections à *Klebsiella pneumoniae* (pneumobacille de Friedländer); (iii) la streptomycine dans les infections liées aux bactéries gram-négatives d'origine intestinale; (iv) la streptomycine dans les infections à *Pseudomonas aeruginosa* (bacille pyocyanique); (v) la streptomycine dans la fièvre typhoïde et les salmonelloses; (vi) la streptomycine dans les shigelloses; (vii) la streptomycine dans le choléra; (viii) la streptomycine dans les brucelloses; (ix) la streptomycine dans les pasteurelloses; (x) la streptomycine dans l'infection à "*Streptobacillus moniliformis*"; (xi) la streptomycine dans les infections à "*Listerella monocytogenes*"; (xii) la streptomycine dans les infections à gonocoques (*Neisseria gonorrheoe*); (xiii) la streptomycine dans les infections liées aux cocci grampositifs; (xiv) la streptomycine dans l'infection charbonneuse; (xv) streptomycine et diphtérie; (xvi) streptomycine et infections à germes anaérobies; (xvii) la streptomycine dans les infections intestinales; (xviii) la streptomycine dans les infections hépato-biliaires; (xix) la streptomycine dans les infections urinaires; (xx) la streptomycine dans les infections génitales; (xxi) la streptomycine dans les infections pulmonaires non tuberculeuses; (xxii) streptomycine et péritonites chirurgicales; (xxiii) streptomycine et affections chirurgicales diverses; (xxiv) la streptomycine en neuro-chirurgie; (xxv) la streptomycine en oto-rhino-laryngologie; (xxvi) la streptomycine en ophtalmologie; (xxvii) la streptomycine dans la tuberculose; (xxviii) la streptomycine dans la lèpre; (xxix) la streptomycine dans les spirochétoses; (xxx) la streptomycine dans les infections à ultra-virus, dans les infections à pleuropneumonia, dans les rickettioses et dans les infections à protozoaires; (xxxi) streptomycine et affections diverses. Bibliography.

Ten years ago there was but one antibiotic of practical therapeutic value; today there are four of paramount importance and nearly two hundred others which, either because of their limited chemotherapeutic effect, their inactivation by serum, or their toxicity, have not as yet found a place in the treatment of human diseases. So rapid has been the development of antibiotic therapy that it would now be almost impossible to keep abreast of every development were it not for the appearance of books such as this volume by Dr Morin and his collaborators from the Clinique des Maladies Infectieuses of the Paris Faculty of Medicine. This work of more than 500 pages is briefly introduced by Professor Mollaret, after which there are chapters on the history, production and chemistry, and general properties of streptomycin. The next two chapters deal with other antibiotics produced by *Streptomyces griseus* and the amounts present in the urine. The titration of streptomycin, its in vitro action, and its pharmacology, are then considered, together with the methods of application, toxicity, and the development of bacteria resistant to streptomycin.

Thereafter the action of the antibiotic on specific infections is considered. Of special value is the long and detailed chapter on tuberculous infections. This chapter, like many others, contains a large amount of original work carried out in the authors' own clinic; in addition, many Continental observations not readily available to readers in Britain are ably summarized. Not the least valuable feature of this important volume is a bibliography of 30 pages, the full titles of the original papers being given. This book will be indispensable to all those who are working or propose to work on streptomycin. There are only two possible criticisms: firstly, as with so many French books, there is no index, and secondly, the binding is so bad that in a very short space of time the cover comes adrift and the book begins to disintegrate.

G. M. Findlay

HISTORY AND BIBLIOGRAPHY

1614 Tom Cullen of Baltimore

Judith Robinson. Toronto: Oxford University Press; London: Geoffrey Cumberlege, 1949. xii + 435 pages; 20 illustrations. 24 × 16 cm. £1 5s. [£1.25]

Part I. Canadian preparation. Part II. Hopkins beginnings. Part III. Continuing in Baltimore. Part IV. Achievements. Part V. The fighting years. Part VI. "What's best for the patient . . ." Part VII. Getting things done. Appendix: published works. Index.

This handsome production of the Toronto branch of the Oxford University Press, written by a Toronto journalist, is addressed to the general public, but should not be missed by anyone interested in gynaecology, in echoes of Osler, or in the growth of the Johns Hopkins Hospital and its Medical School and Bulletin. The subject of this biography is the discoverer of "Cullen's sign", the inventor of the forceps bearing his name, and the author of the now classical books on cancer of the uterus, adenomyoma of the uterus, myoma of the uterus, and the embryology, anatomy and diseases of the umbilicus. His many papers bear witness to his belief in publication—not for its own sake, but for permanent record and in order to pass on results to both research workers and clinicians; this belief was also largely responsible for the valuable volumes of collected papers of his department.

The critical reader may in this case profitably look beyond journalese and over-emphatic chapter titles to the account of the achievements of this great surgeon and teacher and of the developments in his field and in Johns Hopkins which have coincided with his long and fruitful career. When young Tom Cullen finished a year's internship in the Toronto General Hospital, he had the opportunity to assist at an operation performed by Dr Howard Kelly, gynaecologist-in-chief of Johns Hopkins; that experience turned him from medicine to surgery, and with characteristic decision he immediately obtained the promise of a junior internship with Kelly. The next September he started humbly enough on his work among the giants of Hopkins' early days—the head of the medical department was another Canadian, Dr William Osler—with a preliminary three months in pathology, under William H. Welch. Cullen was later to refuse offers from elsewhere of greater seniority and reward, in order to stay with the department of gynaecology at Hopkins; in 1938 he retired from its direction at the age of seventy—a retirement which was an expansion into even fuller public activities than before. Since then the Johns Hopkins' Professor Emeritus of Gynaecology has returned once or twice each year, at the invitation of his successor, to conduct his operative clinics. Although he has a reputation as a great teacher, Professor Cullen himself claims he has never "taught" students: "I just try to show them what there is to learn. It's all anybody can do."

This is the story of a life bridging several generations and two worlds—the present with that nostalgic past when an impecunious young transatlantic research worker not only successfully controverted von Recklinghausen, but at a day's notice left for a spring and summer in Europe, where he visited Leyden and Göttingen, learned German by using it, and worked in the laboratory of Johannes Orth, *Lieblingsschüler* of Virchow. It is also a book full of the charm and vitality of its central figure and the ceaseless flow of his anecdotes about colleagues, patients, and plain people. It can hardly fail to interest anyone who reads it.

H. P.

1615 The Healing Touch

Harley Williams. London: Jonathan Cape, 1949. 408 pages; 8 illustrations. 20 × 14 cm. 15s. [£0.75]

Part 1. Three royal physicians. (i) Sir William Knighton, Bart.; (ii) Sir James Clark, Bart.; (iii) Sir William Jenner, Bart. Part 2. Two prophets. (i) Sir Edwin Chadwick; (ii) Thomas Southwood Smith. Part 3. Florence Nightingale. Part 4. Charles Edouard Brown-Séquard. Part 5. A new world of medicine. References.

The "healing touch" of which Dr Harley Williams writes is an "instinctive faculty" which "can produce prodigious improvements in our tough human material." He has selected a series of remarkable men and women (not all doctors) of the last century and a half, in whom this faculty expressed itself and who, through their personality, influenced medical progress and altered the attitude of ordinary people to health and sickness. The book is written for non-specialist readers and is superficially a piece of journalism, chatty and sometimes cheap. It is, however, more serious than at first appears. Dr Williams is attracted by contrasts, both within the individual and in historic relationships, and his character sketches are in consequence vivid if not profound. He ranges from court physicians, with little scientific knowledge but with a gift for managing such august and difficult patients as George IV and Queen Victoria, to the self-effacing Mayo brothers, who devoted their lives to the development of a first-class surgical centre in the Middle West. Between these extremes he sketches the English prophets of the new hygiene, Edwin Chadwick, Thomas Southwood Smith, and Florence Nightingale, and the cosmopolitan conjurer of physiology, Brown-Séquard, a character of contradictions after Dr Williams' heart.

A startling and tragic contrast is the story of the Prince Consort's death. Ignorance of proper nursing was a contributory factor, yet only a year earlier Florence Nightingale had sent Queen Victoria, who knew and admired her, a copy of *Notes on nursing* which was intended to make the essentials of nursing clear to every educated woman. Dr Williams tells the story and points the moral admirably.

Many great figures make brief appearance between the principal actors. Florence Nightingale, with her fanatical sense of vocation, is contrasted with Elizabeth Fry, who led a full normal life while carrying on her philanthropic work in the prisons. The mystic Southwood Smith was a devoted disciple of the extravagantly matter-of-fact Bentham. Brown-Séquard, born in Mauritius of mixed French and Irish-American parentage, moving feverishly between France, England and America, was the successor of Claude Bernard, who lived for his small laboratory.

The chapter on the Mayo brothers summarizes the story of modern surgery and includes a clever thumb-nail impression of John B. Murphy, and more extended appreciations of Virchow and Billroth, of "Popsy" Welch, William Stewart Halstead and Harvey Cushing.

W. R. Le Fanu

1616 Hindu Medicine

Henry R. Zimmer. Edited by Ludwig Edelstein. Baltimore: Johns Hopkins Press; London: Geoffrey Cumberlege, Oxford University Press, 1948. lxxii + 203 pages. 20 × 14 cm. £1 12s. [£1.6]

Introduction. (i) Medical tradition and the Hindu physician; (ii) the human body: its forces and resources. Notes to Introduction. Notes to Chapter i. Notes to Chapter ii. Index of passages.

The late Professor Zimmer gave the Hideyo Noguchi lectures at the Johns Hopkins Institute of the History of Medicine in 1940. When Zimmer died on 20 March 1943, the first lecture and most of the second had been extensively revised and rewritten, but there were only brief notes on the problems to be dealt with in the third chapter. Dr Ludwig Edelstein who edited this material has had the first two lectures printed as they stood.

The first lecture is concerned with medical tradition and the Hindu physician. It describes the complexity of magic cures; the many-sided approach to the disease-demon; the elaborate spells to ensure the complete effectiveness of amulets, special foods, and ceremonial gestures; and, throughout the cure, the appeal by suggestion to the patient, who is made aware of the whole process and progress of healing. A hymn of 28 stanzas, part of a medical rite for cases of consumption, is translated and annotated, as is a long chant from the Vedic pharmacopoeia. An important asset of the Hindu magician-physician was his ability to league himself with all the divine healing forces. He could call upon the divine powers and spiritual energies of all the herbs he used. The close relationship of religious philosophy—there was no other philosophy—with medicine is reflected in the Four Noble Truths of Buddhism, which correspond exactly to the four successive problems that the physician must formulate and solve in treating any patient. The works of Suśruta in the fourth century and Caraka in the first century A.D. differed only in essentials from the 17th century Jīvānanda and all three show Hindu medicine and surgery as an integral part of philosophy and religious life.

This first lecture, which sets medicine against the wide cultural background, leads naturally to the second lecture—on the Hindu

view of the human body. The body, like the whole universe, is held to be a manifestation of divine substance and energy, and its principal faculties and forces are the microcosmic counterpart of all the powers and processes in the world. This concept and its variations are traced from pre-Aryan antiquity to the latest classic system of the Tantras and to the technique of Yoga, which is intended to bring into consciousness the essence of the five elements —aether, air, fire, water, and earth. This correspondence between microcosm and macrocosm is important in Hindu medicine. The three humours, for example, wind, bile, and phlegm, represent three divine universal forces, wind, sun, and moon. The aim of the Yoga adept is to fill with concentrated wind or life-breath the two channels which begin at the nostrils, and, crossing and entwining the spinal column, descend to the sacrum. One channel is related to the lunar and the other to the solar forces. Hindu medicine lists five kinds of life-breath, Yoga ten, and none of them is related to the lungs—the principal seat of phlegm. The three humours and the blood share the 700 tubular vessels in the body, all of them taking origin from the navel. After analyzing this schematic speculative anatomy, Zimmer goes on to compare Greek medicine in its most dynamic phase with the static conservatism of traditional Hindu medicine. Greek and Hindu beliefs about generation and gestation are also contrasted; there, unfortunately, the unfinished second lecture ends abruptly.

This is a book that no one who is interested in the history of medicine can neglect. It is fragmentary and unfinished. There are omissions and repetitions, and a number of interpretations which are not likely to meet with general acceptance. Yet it is impossible to reach the last page without a feeling of frustration and deep regret —frustration because this is the beginning and the middle only of an important thesis, regret because Zimmer was not spared to write the third and last section.

I.H.F.

1617 Discoverers for Medicine

William H. Woglom. New Haven, Conn.: Yale University Press; London: Geoffrey Cumberlege, 1949. x + 229 pages; 14 illustrations. 24 × 16 cm. 18s. [£0.9]

(i) Introduction; (ii) the blood pressure; (iii) respiration; (iv) the foxglove; (v) vaccination; (vi) the laryngeal mirror; (vii) the Eustachian tube; (viii) eyeglasses and spectacles; (ix) the itch; (x) quinine; (xi) phagocytosis; (xii) X rays; (xiii) heredity; (xiv) milk sickness. Bibliography. Index.

The meaning of the rather curious title which Dr Woglom has given his book becomes plain only after his introduction is read. The author has set out to give an account of some of the notable contributions made to medicine by laymen, and the preposition in the title is intended to suggest this distinction. In most of the 14 separate studies in this volume the discovery is credited to an individual; e.g., Stephen Hales (blood pressure), Manuel Garcia (the laryngeal mirror), and Benjamin Franklin (spectacles). In others, it is attributed to the vast anonymous herd who sustain and enlarge popular tradition; e.g., the folk tradition about the use of the foxglove, cowpox inoculation, etc.

It is an interesting conception, and the natural antithesis to the many studies of the debt that is owed to medical men by workers in other fields. Unfortunately, this book fails to convince us that any new light can be thrown on medical history by such an approach. As the bibliographies at the end of the book indicate, all the subjects dealt with here have been studied in greater detail elsewhere, so that this book will interest the general reader or the student rather than the historian who is already acquainted with the standard works on the subject.

In spite of the author's persuasive introduction it is debatable how far such figures as Metchnikoff, Roentgen, Hales, or Pasteur (who is omitted here) can be regarded as "laymen". Hales was as much a physiologist as any occupant of a modern chair; the only distinguishing factor is that he did not earn a living by his physiological studies but as the "perpetual curate of Teddington". Roentgen, already a celebrated physicist when he discovered *x* rays, made a discovery within his own field of knowledge. That its applications have been so momentous in the advance of medicine is due to the work of medical men (e.g., Cannon) who immensely extended the range of its usefulness. Metchnikoff is not the only biologist whose work has forwarded medical knowledge. Surely it shows a lack of historical perspective to regard such men as amateurs. The fact that they were not doctors of medicine with diplomas duly signed and sealed seems quite unimportant.

As for the non-professional laymen such as Jesty, and the first unknown herb-gatherers who discovered the virtues of foxglove, how does their "work" compare with that of the medical men who established vaccination and digitalis in regular medical practice? We are told, a point overlooked by Dr Woglom, that country women in Ireland 100 years ago used the mould *penicillium* for cuts and wounds, but should they be set beside Fleming and Florey as "discoverers"?

But perhaps this is captious criticism of a very readable book which, while adding nothing to our knowledge, gives useful short accounts of the background of a number of important medical advances. The book is a product of the widespread interest in medical history in the United States and was originally published by the Yale University Press.

F. N. L. Poynter

PARTICULARS OF BOOKS REVIEWED ELSEWHERE IN THIS NUMBER

The numerals in square brackets are the serial numbers of the articles in which these books are reviewed

[1539] Antibiotics : a Survey of Penicillin, Streptomycin, and Other Antimicrobial Substances from Fungi, Actinomycetes, Bacteria, and Plants. Vols. I & II

H. W. Florey, E. Chain, N. G. Heatley, M. A. Jennings, A. G. Sanders, E. P. Abraham, M. E. Florey. London : Geoffrey Cumberlege, Oxford University Press, 1949. xxii + 1774 pages ; 265 figures. 25 × 16 cm. £8 8s. [£8.4]

Vol. I : Part I. (i) Historical introduction. Part II. General experimental methods. (ii) Detection and extraction of antibacterial substances ; (iii) the assay of antibiotics ; (iv) methods for measuring the sensitivity of micro-organisms to antibiotics ; (v) antibiotics in differential culture media. Part III. Antibiotics from fungi—general considerations. (vi) Review of species examined. Part IV. Antibiotics from fungi—substances other than penicillin. (vii) Substances produced by fungi imperfecti and ascomycetes ; (viii) substances produced by basidiomycetes, phycomycetes, and unidentified fungi. Part V. Antibiotics from actinomycetes. (ix) Substances other than streptomycin. Part VI. Antibiotics from bacteria. (x) Antibiotics from bacteria in the genus *Bacillus* ; (xi) antibiotics from other bacteria ; (xii) antibiotics from chromogenic bacteria. Part VII. Antimicrobial substances from lichens, algae, and seed plants. (xiii) Substances from lichens and algae ; (xiv) substances from seed plants. Vol. II : Part VIII. Penicillin. (xv) Historical introduction ; (xvi) penicillin-producing fungi ; (xvii) the production of penicillin ; (xviii) extraction and purification of penicillin ; (xix) metabolic changes during penicillin fermentation ; (xx) the chemistry of penicillin. Historical introduction ; (xxi) physical and chemical properties of the penicillins ; (xxii) the components of the penicillin molecule ; (xxiii) hydrogenolysis products of penicillin ; (xxiv) penicillin sulphone, penicillin sulphoxide, and the thiocyanate derivative of penicillin ; (xxv) products of isomerization of the penicillins ; (xxvi) thiazolidines and β-lactams ; (xxvii) the structure of the penicillin molecule ; (xxviii) attempts to synthesize the penicillins ; (xxix) modifications of *p*-hydroxybenzylpenicillin ; (xxx) biogenesis of penicillin ; (xxxi) the activity of penicillin against micro-organisms ; (xxxii) methods of testing material containing penicillin for sterility ; (xxxiii) penicillinase ; (xxxiv) acquired resistance of micro-organisms to penicillin ; (xxxv) the action of penicillin on micro-organisms ; (xxxvi) the combined action of penicillin with other drugs ; (xxxvii) the pharmocology of penicillin. Toxicity ; (xxxviii) the pharmacology of penicillin. Absorption ; (xxxix) the pharmacology of penicillin. Distribution in the body ; (xl) the pharmacology of penicillin. Excretion and loss in the body. Part IX. Streptomycin. (xli) Production and isolation of streptomycin ; (xlii) chemical properties and structure of streptomycin ; (xliii) the activity of streptomycin and dihydrostreptomycin against micro-organisms ; (xliv) acquired resistance of micro-organisms to streptomycin : the action of streptomycin ; (xlv) the pharmacology of streptomycin and dihydrostreptomycin ; (xlvi) mannosidostreptomycin (streptomycin B), other streptomycins, and streptomycin residues. Part X. (xlvii) The action of antibiotics on bacteria. Part XI. (xlviii) Conclusions. Appendix and tables of antibiotics. Bibliography. Author index. Subject index.

[1541] Publicaciones del Instituto de Historia de la Medicina. Vol. XII, Nos. I & II

Aníbal Ruiz Moreno. Buenos Aires : Universidad de Buenos Aires, Facultad de Ciencias Médicas, 1948. No. I : 204 pages. 24 × 17 cm. No. II : 151 pages. 24 × 17 cm.

No. I : *Obras de Galeno.* (i) Advertencia ; (ii) compendio del pulso para los estudiantes ; (iii) de las diferencias de pulsos ; (iv) indice de temas ; (v) indice de autores citados y otros nombres propios ; (vi) indice de referencias a otras obras de Galeno ; (vii) vocabulario de términos técnicos.

No. II : *Tratado de la viruela y el sarampión por Abū Bakr Muhammad Ibn Zakarīyā (Razés).* (i) Vida y obras de Razés ; (ii) estudio de la obra ; (iii) Kitab Al-Jadari Wa-Al Hasba (tratado de la viruela y el sarampión) ; (iv) referencias sobre viruelas y sarampión, que se encuentran en el Kitab Al-Mansuri ; (v) referencias sobre viruela y sarampión que se encuentran en Divisio Morborum ; (vi) referencias sobre viruela y sarampión que se encuentran en Kitab Al Hawi. *La Sanidad militar en la guerra del Brasil.* (i & ii) Consideraciones generales ; (iii) organización de la campaña sanitaria ; (iv & v) la acción de armas decisiva. Ituzaingó. Apéndice.

[1545] Paul Ehrlich

Martha Marquardt. With an introduction by Sir Henry Dale. London : William Heinemann Medical Books Ltd., 1949. xx + 255 pages ; 52 illustrations. 22 × 14 cm. £1 5s. [£1.25]

(i) Childhood and schooldays ; (ii) at the University ; (iii) at the Charité Clinic, Berlin ; (iv) research with Robert Koch and Emil von Behring ; (v) the Steglitz Institute ; (vi) the Frankfurt 'Serum-Institute' ; (vii) the 'side-chain' theory ; (viii) an evening at home ; (ix) 'side-chains' and 'magic bullets' ; (x) stimulants and diversions ; (xi) lectures and publications ; (xii) serumtherapy and chemotherapy ; (xiii) the Georg Speyer-Haus ; (xiv) atoxyl and other arsenicals ; (xv) personal characteristics and the Nobel prize ; (xvi) 606 ; (xvii) invention of 606 announced to the world ; (xviii) Salvarsan—early troubles ; (xix) Königsberg Congress and later troubles ; (xx) Ehrlich and his grandchildren ; (xxi) more discoveries in syphilis ; (xxii) Ehrlich's sixtieth birthday ; (xxiii) honours and appreciation ; (xxiv) slander and libel ; (xxv) the final year.

[1546] The Personality of William Harvey

Geoffrey Keynes. London : Cambridge University Press, 1949. 48 pages ; 8 illustrations. 19 × 13 cm. 5s. [£0.25]

(i) The personality of William Harvey ; (ii) abbreviated list of authorities ; (iii) illustrations.

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Shorter Notices

Trends in Medical Education. The New York Academy of Medicine Institute on Medical Education, 1947

Edited by *Mahlon Ashford*. New York: The Commonwealth Fund; London: Geoffrey Cumberlege, 1949. xiv + 320 pages. 22 × 14 cm. £1 4s. [£1.2]

The Committee on Medical Education of the New York Academy of Medicine held six conferences on medical education in April 1947; more than fifty prominent persons were present, and this volume records the fruits of their deliberations. The contributors include deans and professors in medical schools, specialists in all branches of medicine, general practitioners, and even educationalists concerned with future medical students in secondary schools and universities. It is not, therefore, surprising to find that the book contains diverse and irreconcilable opinions; indeed, there are perhaps more points of disagreement than the reverse.

Some conclusions, however, do emerge: there is no doubt that in American medicine specialization is increasing and that the undergraduate and postgraduate programmes are changing and will be further modified to meet the requirements of the would-be specialist. This is, of course, most striking in the postgraduate field; carefully graduated courses of five years and longer are being followed by increasing numbers of neophytes aspiring to the accolade of specialism.

The discussion reflects a considerable degree of uncertainty about the role of the general practitioner; there is general agreement that the family physician is necessary, but considerable doubt about what he should do and even graver uncertainty as to how he should be trained. The development of group practice in the smaller communities might, some contributors felt, be the logical step in the further evolution of medical practice.

The book gives an excellent cross-section of American conditions and opinions in this field which is the scene of so much controversy. Medical educators in countries other than the USA will find it useful to compare and contrast with their own experiences and opinions.

D. F.

Tuberculosis Nursing

Jessie G. Eyre. London: H. K. Lewis & Co. Ltd., 1949. xii + 291 pages; 103 illustrations. 22 × 14 cm. £1 1s. [£1.05]

This comprehensive and well-illustrated book, by the Senior Sister Tutor of St. Helier Hospital, Carshalton, England, fills a gap in nursing literature. It is intended as a guide to those wishing to gain additional postgraduate experience or to specialize in tuberculosis nursing. The author gives considerable attention to collapse therapy and chest surgery, in which branches the modern treatment of pulmonary tuberculosis has most developed; the care of the patient in hospital is also dealt with. Other chapters of special interest are those on chemotherapy (including the use of streptomycin, calciferol and *para*-aminosalicylic acid), on tuberculosis of bones and joints, and on the care and after-care of tuberculous patients.

H. M. C.

Food Inspection Notes. A Handbook for Students

H. Hill & F. Dodsworth. Third edition. London: H. K. Lewis & Co. Ltd., 1949. viii + 125 pages; 17 × 11 cm. 7s. 6d. [£0.375]

This little book is addressed primarily to the student food inspector. Its aim is to give him the essentials of food inspection in concise form and in this it succeeds admirably. As the title suggests, the material is set out in note form throughout. The first half of the book is devoted to meat inspection under the headings of ante-mortem inspection, slaughter-houses, slaughtering and dressing, anatomy and physiology, and diseases of animals. This last section is particularly useful. Each disease is briefly but clearly described and in each case the description concludes with a "judgment," i.e. action to be taken by the food inspector. To give just two examples, for rheumatism the "judgment" is: "Consider on merits. Joints affected, removed and condemned. If general emaciation, carcase and organs condemned", and for anthrax: "Notifiable disease, special Order. Carcase and organs condemned."

The second half of the book deals with the examination of poultry, game, milk, canned foods and miscellaneous foods. The chapter dealing with food-poisoning is not up to the standard of the rest of the book and requires bringing up to date. It is not now true that canned meat and salmon are the commonest causes of poisoning by the Salmonella group, or that the staphylococcus is only occasionally a cause of food poisoning. The last chapter deals briefly with the technique of food sampling.

The book has the great merit of being essentially practical in its approach. The authors have concentrated upon providing the facts which the practising food inspector must know. This, coupled with the arrangement in note form, means that the book cannot be, and is not intended to be, a substitute for a textbook. The handling of food is of course mentioned incidentally in various places, but in view of its increasing importance it would merit a special chapter in future editions.

It is clearly impossible for a book of this type to deal adequately with legislation and the authors have chosen to omit this altogether. Nevertheless, the food inspector works in practice within the framework of legislation and must always keep in mind his legal duties and legal powers. For this reason, the value of the book to the student would be enhanced if the relevant legislation were cited, say, as footnotes.

D. B. Bradshaw

Meet Yourself at the Doctor's

Mass-Observation, with drawings by *Ronald Searle*. London: The Naldrett Press, 1949. 70 pages; 20 illustrations. 19 × 12 cm. 3s. 6d. [£0.175]

After a spate of publications concerning the National Health Service, its administration, its legal aspects, its finances and the first year's working, this attempt to evaluate the reactions of men and women of all classes is illuminating and amusing. There are comments made by the public before and after the adoption of the Act; there is a comparison of the points of view of Dr D. and Dr Y., and the story of the doctor's working day. One chapter reports on conversations heard in the waiting-room and another on accounts by patients of procedure inside the surgery. The attitude of mothers to the infant-welfare service and the protests of those who still prefer such alternatives to state medicine as osteopathy and Christian Science are also dealt with. Against evidence of overwork and waste of time and money has to be set a woman's comment, "It's everything to a mother to know that you can call the doctor even when you haven't the money ready." Written with serious intention, the text and conversations present a well-balanced assessment of human reactions, to which Ronald Searle's illustrations give gaiety.

H. M. C.

Gas and Air Analgesia

R. J. Minnitt. Fourth edition. London: Baillière, Tindall & Cox, 1949. vii + 86 pages; 22 figures; 18 × 12 cm. 5s. [£0.25]

The 4th edition of this excellent handbook for midwives has now been published. As would be expected from the originator of the method, it is authoritative and contains all that the midwife needs to know. It will also prove useful to those anaesthetists entrusted with the preparation of lectures to midwives on analgesia.

The text remains substantially the same as that of the previous editions except that some of the details of technique have been elaborated. The latest regulations of the Central Midwives Board have been included. The print, paper, illustrations and binding are alike excellent, and the book should be able to withstand the hard wear to which it will doubtless be subjected.

C. Langton Hewer

Temas de Tisiología

José F. Verna et al. Cordoba, Argentina: Imprenta de la Universidad, 1949. 271 pages; figures. 23 × 16 cm.

Professor Verna and his associates are to be congratulated on this volume; they have succeeded in presenting a group of papers on tuberculosis, ranging from the technique of thoracoplasty to the radiology of intestinal tuberculosis. The first paper, by Professor Verna, deals with pulmonary tuberculosis and cancer; he points out that pulmonary tissue already damaged by tuberculous infiltration is not less favourable to the growth of neoplasm than any other tissue equally damaged by a pathological process. Although tuberculosis may develop in a neoplastic lesion, the reverse process is more frequent. Tuberculosis may establish a predisposition to cellular metaplasia, and once both processes are co-existent, their further evolution is somewhat independent of each other. It has been found that carcinoma grows more readily on tuberculous lesions which are still active; this is perhaps due to the scanty or absent fibrous tissue reaction of the active lesion.

After a discussion of the relationship between tuberculosis and climate by Professor Sarmiento, Professor Sonzini describes the anatomy and surgical technique of thoracoplasty, following the principles expounded by Finochietto and his colleagues in Argentina. This operation stresses separation rather than division of muscles; it has not met with much enthusiasm in Britain, as ample exposure is considered far more important than the avoidance of muscle splitting. Professor Menso gives a brief review of intrathoracic pathology and lung resection, and there is also a short paper on Kahn's reaction in plasma, by Dr Manavella. In his paper on the re-inoculation of the previously tuberculinized guinea-pig, Dr Astrada reaches the interesting conclusion that tuberculin diminishes the phagocytic power of leucocytes against the tuberculous organism, rendering the animal more susceptible to the action of the injected germ.

The paper on the radiology of intestinal tuberculosis, by Professor Moreno, is well presented, and deals with the differential diagnosis of this condition. The various other papers which complete the volume are also of great interest; the book will no doubt be eagerly read by many workers, both laboratory and clinical, in the field of tuberculosis.

A. J. Coello

Books Received

September 1949—January 1950

Reviews of many of these books appear in this number of the Bulletin or will appear in future numbers

Allen, C. *The sexual perversions and abnormalities. A study in the psychology of paraphilia.* 2nd ed. 1949. Geoffrey Cumberlege, Oxford University Press (London), £1 5s. [£1.25]

Ashford, M., editor. *Trends in medical education. The New York Academy of Medicine Institute on Medical Education, 1947.* 1949. Commonwealth Fund (New York); Geoffrey Cumberlege, Oxford University Press (London), 24s. [£1.2]

Banks, H. S. *The common infectious diseases. A handbook for students and postgraduates.* 1949. Arnold (London), £1 1s. [£1.05]

Barach, J. H. *Diabetes and its treatment.* 1949. Oxford University Press (New York); Geoffrey Cumberlege (London), £4

Barrow, D. W. *The clinical management of varicose veins.* 1949. Cassell (London), £1 5s. [£1.25]

Beaumont, G. E. *Applied medicine.* 1950. Churchill (London), £1 10s. [£1.5]

Bernard, E., Kreis, B. & Lotte, A. *Traitement par la streptomycine de la méningite tuberculeuse, de la tuberculose des voies respiratoires, et de la tuberculose ostéo-articulaire chez l'adulte.* 1949. L'Expansion Scientifique Française (Paris)

Berning, H. *Die Dystrophie.* 1949. Thieme (Stuttgart), 18 Mk.

Bibliographia Medica Helvetica. Vol. 5, 1947. 1949. Schwabe (Basle), 20 Sw. fr.

Biochemical Society. *Partition chromatography.* (Biochemical Society Symposia No. 3.) Organized and edited by R. T. Williams, assisted by R. L. M. Synge. 1949. University Press (Cambridge), 6s. [£0.3]

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Bourne, A. *A synopsis of obstetrics and gynaecology.* 10th ed. 1949. Wright (Bristol), £1 1s. [£1.05]

Bourne, G. H. *How your body works.* 1949. Sigma (London), 12s. 6d. [£0.625]

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British Empire Cancer Campaign. *Twenty-sixth annual report covering the year 1948.* [1949] British Empire Cancer Campaign (London)

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Chatton, M., Margen, S. & Brainerd, H. D. *Handbook of medical management.* 1949. University Medical Publishers (Palo Alto, California), $3

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Clark, W. E. Le G. *Practical anatomy.* 2nd ed., revised and rewritten. 1949. Arnold (London), £1 10s. [£1.5]

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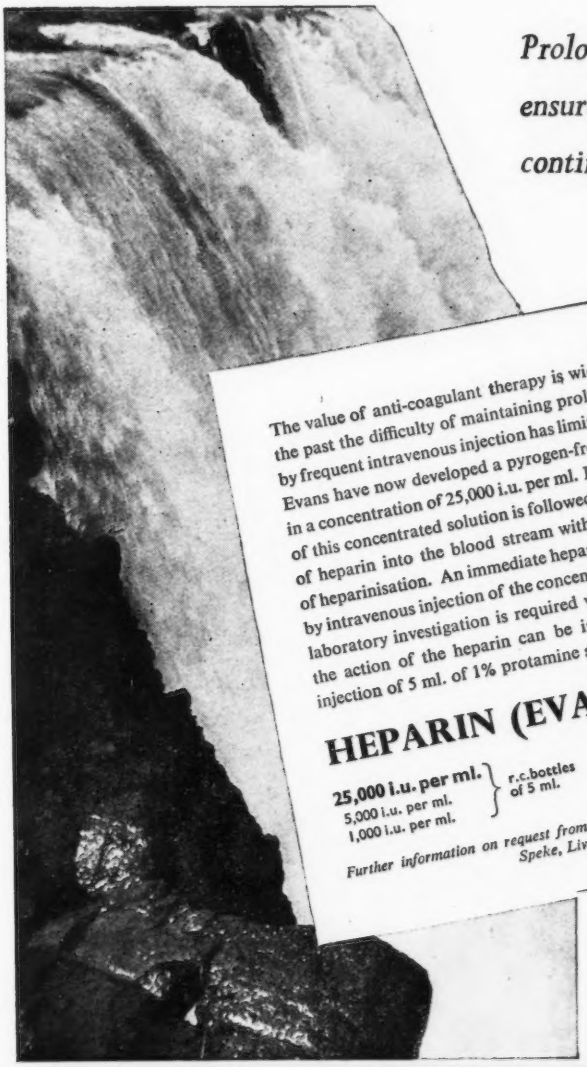

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